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Soft tissue phenotype modification predicts gingival margin long-term (10-year) stability: Longitudinal analysis of six randomized clinical trials

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ABSTRACT

Aim: To assess the prognostic value of soft tissue phenotype modification following root coverage procedures for predicting the long-term (10-year) behavior of the gingival margin.

Materials and Methods: Participants from six randomized clinical trials on root coverage procedures at the University of Michigan were re-invited for a longitudinal evaluation. Clinical measurements were obtained by two calibrated examiners. A data-driven approach to model selection with Akaike information criterion (AIC) was carried out via multilevel regression analyses and partial regression plotting for changes in the level of the gingival margin over time, and interactions with the early (6-month) results of soft tissue phenotypic modification.

Results: One hundred and fifty-seven treated sites in 83 patients were re-assessed at the long-term recall. AIC-driven model selection and regression analyses demonstrated that 6-month keratinized tissue width (KTW) and gingival thickness (GT) influenced the trajectory of the gingival margin similarly in a concave manner; however, gingival thickness (GT) was the driving determinant that predicted significantly less relapse in the treatments, with stability of the treated gingival margin obtained beyond values of 1.46 mm.

Conclusions: Among a compliant patient cohort, irrespective of the rendered therapy, the presence of at least 1.5 mm KTW, and 1.46 mm GT was correlated with the long-term stability of the gingival margin.

Key words: Soft tissue augmentation, Periodontitis, Gingival recession, Evidence-based dentistry, Phenotype, Root coverage

Clinical relevance

Scientific rationale for study. To identify prognostic factors from early (6-month) outcomes of root coverage procedures to predict the long-term behavior of the level of the gingival margin post treatment.

Principal findings. Soft tissue phenotype modification following a root coverage procedure influences the long-term behavior of the gingival margin, in particular, obtaining a gingival thickness (GT) of 1.46 mm at 6 months in the presence of at least 1.5 mm keratinized tissue width (KTW) was shown to predict a stable level of the gingival margin over a period of 10 years.

Practical implications. Among the goals of root coverage procedures, the achieving of at least 1.5 mm KTW and 1.5 mm GT should be targeted to provide long-term stability of soft tissue augmentation therapy.

1. Introduction

The long-term clinical outcome is one of the most crucial and determining factors when choosing a specific therapy (Cortellini, Buti, Pini Prato, & Tonetti, 2017; G. P. Pini Prato, Di Gianfilippo, & Wang, 2019). Relative to root coverage procedures, the long-term outcomes of different techniques are of great interest in the scientific community and among practicing clinicians (G. P. Pini Prato, Magnani, & Chambrone, 2018; Rasperini et al., 2018; Tavelli, Barootchi, et al., 2020).

Recent studies have been published on the long-term behavior of the gingival margin after root coverage procedures, and the outcomes of the initial therapies overtime (Barootchi et al., 2019a; Petsos et al., 2020; Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Zuhr et al., 2021). In particular, the clinical parameters of keratinized tissue width (KTW), and gingival thickness (GT) – jointly referred to as the periodontal soft tissue phenotype (Cortellini & Bissada, 2018; Jepsen et al., 2018) – have been highlighted for their influence on the stability of the gingival margin, and for their possible implication to periodontal health (Barootchi, Tavelli, Zucchelli, Giannobile, & Wang, 2020; Kao et al., 2020; Kim, Bassir, & Nguyen, 2020).

It has been suggested that sites with a thin soft tissue phenotype are more prone to development of gingival recessions (or its reoccurrence) (Cortellini & Bissada, 2018; Scheyer et al., 2015) and that their modification may increase tolerance against some of the etiologic factors of gingival recessions, such as resuming traumatic toothbrushing habits in non-compliant individuals (Barootchi et al., 2020; Chambrone et al., 2019; Chambrone & Tatakis, 2015; Tavelli, Barootchi, Di Gianfilippo, et al., 2019). In fact, this may explain the relatively high incidence of recession relapse observed in studies that employed a coronally advanced flap (CAF) alone for the treatment of gingival recessions (Barootchi et al., 2019a; Chambrone et al., 2019; G. P. Pini Prato, Magnani, et al., 2018; Tavelli, Barootchi, Cairo, et al., 2019). Thus, the combined use of grafting materials to achieve phenotype modification, may not only improve early root coverage outcomes, but also the long-term results, and the maintenance of the gingival margin over time (Barootchi et al., 2020; Chambrone & Tatakis, 2015; Tavelli, Barootchi, Di Gianfilippo, et al., 2019).

Recently, studies have suggested that soft tissue attributes such as KTW, and GT, among others can individually affect the long-term course of a root coverage-treated gingival margin (Barootchi et al., 2019a; G. P. Pini Prato, Franceschi, Cortellini, & Chambrone, 2018; Rasperini et al., 2018; Tavelli, Barootchi, Cairo, et al., 2019). Despite the significance of these reports, as it relates to daily applicability, KTW, GT or other factors at each tooth can be simultaneously present, absent, or vary relatively in quantity, and even imply the results of different treatments (Barootchi et al., 2020).

To the best of our knowledge, no study has yet reported the longitudinal assessment of previous root coverage treatments on a large-scale, with the application of a joint analysis to simultaneously assess both parameters of the periodontal soft tissue phenotype, and their interrelationship relative to the long-term behavior of the level of the gingival margin. Thus the aim of the present study was to assess the prognostic value of soft tissue phenotype modification following root coverage procedures for predicting the long-term (10-year) behavior of the gingival margin.

2. Materials and Methods

2.1. Study design and participants

The present research was designed as a two-point longitudinal observational analysis of previous randomized clinical trials (RCTs) on the treatment of gingival recession defects (GRs) conducted at the Department of Periodontics and Oral Medicine, School of Dentistry, at the University of Michigan. From May 2019 to January 2021, participants from six parallel-design RCTs were individually recontacted and invited for a follow-up visit and clinical re-examination. Details of the original RCTs can be found in their respective reports (Byun et al., 2009; Huang, Neiva, Soehren, Giannobile, & Wang, 2005; Kimble, Eber, Soehren, Shyr, & Wang, 2004; Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Trabulsi, Oh, Eber, Weber, & Wang, 2004; Wang et al., 2014; Wang, Suarez-Lopez Del Amo, Layher, & Eber, 2015), as well as in the Supplementary Appendix. Individual follow-up reports of three of the six clinical trials can also be found elsewhere (Barootchi et al., 2019a; Barootchi, Tavelli, Gianfilippo, et al., 2021; Tavelli, Barootchi, Di Gianfilippo, et al., 2019).

The protocol of this follow-up investigation was registered and approved a priori, by the Western Institutional Review Board (HUM00146261). The current study is in accordance with the Declaration of Helsinki 1975, as revised in 2000, and informed consents were obtained from all participants who were present for the long-term recall. This manuscript is also prepared following the STROBE statement for improving the quality of observational reports (https://www.equator-network.org/reporting-guidelines/strobe/).

2.3. The original interventions and recruitment criteria

The surgical treatments were all performed at the Graduate Periodontics Clinic of the University of Michigan, where all patients had been randomly allocated to receive a root coverage procedure for coverage of GRs.

Three studies employed the coronally advanced flap (CAF), either alone (Huang, Neiva, Soehren, et al., 2005), or with the addition of a connective tissue graft (CTG) (Byun et al., 2009), an Acellular dermal matrix (ADM)(Wang et al., 2014; Wang et al., 2015), or Platelet-Rich Plasma (PRP)(Huang, Neiva, Soehren, et al., 2005). The tunneling approach was utilized in one trial (Tavelli, Barootchi, Di Gianfilippo, et al., 2019), either with CTG or ADM. A guided tissue regeneration (GTR) approach for root coverage was performed in two other studies, one in which GTR had been employed with, or without the addition of Enamel Matrix Derivatives (Trabulsi et al., 2004), and in another in which GTR had been conducted either with (not part of the present study) or without the addition of a bone substitute (Kimble et al., 2004).

All patient recruitment was derived from a population pool at the University of Michigan School of Dentistry, to similarly include systemically and periodontally healthy adults with non-molar, non-mandibular incisor Miller Class I or II (Miller, 1985)/Recession type I (Cairo, Nieri, Cincinelli, Mervelt, & Pagliaro, 2011) gingival recession defects of at least 2 mm in depth. Details on the eligibility criteria of all trials is presented in tabulate form in the Appendix.

Prior to the surgical procedures, all participants received full mouth supragingival scaling, polishing and oral hygiene instructions, and were instructed to maintain an optimal toothbrushing technique to correct improper habits related to the etiology of the GRs (more details presented in the Appendix).

2.4. Clinical examination at the long-term recall

At the terminal follow-up examination, two calibrated study members (SB, RD) performed all clinical measurements as previously described (Barootchi et al., 2019a; Barootchi, Tavelli, Gianfilippo, et al., 2021; Tavelli, Barootchi, Di Gianfilippo, et al., 2019), to include the depth of the gingival recession/level of the gingival margin relative to the cemento-enamel junction (Rec) and keratinized tissue width (KTW), both on the mid-facial region, probing pocket depth (PD), clinical attachment level (CAL), and gingival thickness (GT) approximately 1.5 mm below the gingival margin. Inter- and intra-reliability of the clinical measurements between, and among each examiner (SB, RD) was trained and calibrated through measurement of 15 GRs in 10 individuals who were not part of this study (twice, with at least 15 minutes apart), to achieve excellent reproducibility (Kappa scores above 0.95, additional data presented in the Appendix) (Landis & Koch, 1977).

2. 5. Analysis of risk factors for the long-term (10-year) relapse of the gingival margin

The primary goal of this study was to identify variables that predict longitudinal change in the level of the gingival margin at treated sites. In particular, we considered whether the early results of soft tissue phenotype modification (KTW, GT, and their interaction) at 6 months are prognostic of recession over approximately a 10-year time horizon.

Clinical and patient-level parameters at baseline (time of treatment), early (6 months), and long-term follow-up were retrieved for all available individuals at the long-term recall and gathered in a single spreadsheet. For studies that assessed GT at various points, only measurements pertaining to ~1.5 mm below the gingival margin were used.

Means and standard deviations (SD) were used to descriptively summarize continuous data. To evaluate early predictors of the longitudinal changes in the gingival margin (Rec) at treated sites within patients, multilevel linear regression was used, employing a data-driven approach for model construction based on Akaike information criterion (AIC) (Burnham, 2002).

We considered a series of 26 model structures with various specifications for main effects and interactions predicting longitudinal Rec (mm), using baseline and 6-month Rec (mm), 6-month GT (mm), 6-month KTW (mm), and time (years) since the root coverage procedure as predictors, along with retrieved patient- and site-level attributes (such as age, sex, arch, tooth location). To obtain a systematically defined measure of patients' adherence to professional oral hygiene care (as a proxy for "compliance"), the average number of hygiene/prophy visits for the initial 9 years (since this was unanimously available) after the surgical procedure was calculated for all participants to explore its influence on the long-term outcomes.

The models accounted for the fact that a single patient may have contributed data for multiple sites and multiple time points by creating a variable in the dataset for patients with multiple treated sites, for time point. The treatment type was also controlled for in the analyses (as the original treatments varied across trials). Random effects for patient, site (tooth), treatment type, and study were always included to account for heterogeneity attributable to these factors. Treatment effects were modeled as random rather than fixed effects to permit emphasis on the common risk factors for the long-term relapse/change in the level of the gingival margin across multiple treatments.

GT and KTW were power transformed using functions of the form $\frac{x^p}{p-1}$. The value of the exponent p was estimated from the data and captures relationships between Rec and either GT or KTW, that were either concave or linear, allowing for the possibility that post-treatment gains in GT or KTW may have lesser impact on future Rec when the base level of GT or KTW was higher.

AIC was used for selection of the model that best fit the data (Burnham, 2002), optimizing the AIC over the 26 model structures, and over the transformation parameters for GT and KTW, followed by additional sensitivity analyses for these outcomes, to confirm associations with gingival margin relapse (Rec). Confidence intervals (CI) were produced for fixed effects, and a p value threshold of 0.05 was set for statistical significance. The model selection process, along with a complete list of all models and their corresponding AIC values are shown in the appendix. Partial regression plotting was used to visualize the relationship between the key risk factor(s) and change in Rec (level of the gingival margin) over a 10-year time horizon. Clinically, a maximum change of 0.5 mm in Rec/level of gingival margin at 10 years was assumed to be negligible, to explore interactions of "gingival margin stability" through the intersection of regression line(s).

All analyses were performed in R (Version 1.3.959) by two investigators with expertise in statistical methodology (SB, KS), and the following R packages: tidyr (H. H. wickham, L, 2019), arm (Gelman, 2020), dplyr (H. F. Wickham, R; Henry, L; Müller K, 2019), lme4 (Bates, 2015), merTools (Knowles, 2019), ggplot2 (Wickham, 2016), and ggeffects (Lüdecke, 2018).

3. Results:

3.1. Participants at the long-term recall

Overall, 83 patients (34 males, 49 females), with a total of 157 treated GRs were evaluated at the long-term recall (from 9 to 18 years post-treatment). Figure 1 shows the per-study and per-treatment sample sizes at the follow-up timepoint. General information on the demographics and clinical characteristics of the samples can also be found in Supplementary Table 1 in the Appendix.

Throughout the follow-up period, all participants received professional oral prophylaxis, hygiene care and/or supportive periodontal therapy at least once-yearly (average 1.81 ± 0.38) either at the University of Michigan School of Dentistry ($n = 61$), or at a local private office ($n = 22$). All patients generally showed healthy periodontia at the recall. While none of the recruited participants in the original studies were smokers, at the recall, four patients reported occasional smoking (≤5 cigarettes/day).

3.2. Clinical measurements and descriptive analysis

Table 1 presents descriptive summaries of Rec, KTW and GT at the long-term recall, and their respective measurements at baseline (prior to surgical root coverage), as well as the early root coverage outcomes per study treatment. Table 2 presents the outcomes of mean and complete root coverage for the included studies and treatment arms. Overall, at the long-term follow-up time point, Rec and KTW tended to be higher relative to their levels at 6 months, while the values of GT and PD were qualitatively stable over time.

3.3. Risk factors for the long-term (10-year) relapse in the level of the gingival margin

The model selection process and the AIC results are presented in the Appendix. The best fitting model for explaining the trajectory of Rec throughout time included main effects for time, for power-transformed GT at 6 months, and for time by 6-month GT interaction (Table 3). In this model, Rec changes linearly over time within subjects/sites, with intercept and slope dependent on the 6-month GT value.

GT at 6 months ranged from 0.5 to 2 mm, with greater GT values predicting smaller Rec in a concave manner, meaning that an increase in GT predicted a stronger change in Rec at the lower end of the GT range, with an apparent attenuation of GT's association with gingival margin stability at GT values greater than 1.46 mm, considering a clinically negligible change of 0.5 mm at 10 years (Figure 2). KTW at 6 months ranged from 1.5 to 6 mm, and it was observed after adjusting for 6-month GT, KTW no longer had a statistically significant association with Rec (models 2 and 3, Appendix). However, when excluding GT from the model, KTW predicted the trajectory of the gingival margin in a similar manner to GT (model 3, Appendix). While KTW and GT were only weakly correlated (Pearson correlation 0.12, Appendix), they appear to capture the same information about the trajectory of the gingival margin over time. Finally, a greater increase in Rec was also observed for sites with a greater baseline severity, while the residual Rec at 6 months was not significantly associated with the long-term outcomes.

Residual variation was attributed to multiple factors, as captured by the random effects in the model (Table 3). The site of treatment (tooth) appeared as the dominant level of variation in longitudinal Rec that is not explained by the covariates in the model. Therefore, two adjacent teeth in the same individual could be on either similar or different paths relative to the gingival margin, due to site-specific reasons. Next, there was a tendency for multiple treated teeth in the same individual to be on somewhat similar trajectories (patient random effect of 0.15). The treatment random effect was weaker (0.09), suggesting that the original root coverage approach, while relevant to the early (6-month) outcomes (random effect of 0.07), does not influence the trajectory of Rec, thereafter. Thus, when accounting for site- and patient-specific factors, the slope of Rec is not treatment-type specific.

4. Discussion

The present study aimed to explore the prognostic capacity of the periodontal soft tissue phenotype (KTW and GT) in predicting the long-term behavior of the gingival margin at sites treated with a root coverage procedure. All in all, our data suggest that the long-term trajectory of a treated gingival margin is associated primarily with site-specific phenotypic characteristics (GT, KTW & baseline severity), and secondarily by unmeasured person-level and site-level characteristics. Additionally, the rate of change in Rec with respect to time is similar among treatments, after controlling for GT at 6 months, considering that sites bear at minimum, 1.5 mm of KTW.

In one way or another, the relevance of KTW, and more recently GT to different disciplines of periodontology, have been expressed extensively throughout the literature (Anderegg, Metzler, & Nicoll, 1995; Kennedy, Bird, Palcanis, & Dorfman, 1985; Lin, Chan, & Wang, 2013; Parma-Benfenati, Fugazzoto, & Ruben, 1985; Perussolo, Souza, Matarazzo, Oliveira, & Araujo, 2018; Stetler & Bissada, 1987). More recently, the interest in the concept of the gingival (also referred to as the soft tissue) phenotype has emerged, which encompasses a three-dimensional outlook on the periodontal soft tissues (Cortellini & Bissada, 2018; Jepsen et al., 2018), which along with its modification has accompanied an increasing interest among clinicians and researchers.

Relative to the outcomes of root coverage, previous studies have suggested that these two components (KTW and GT), can influence the final surgical results and/or the long-term level of the gingival margin (Cairo et al., 2016; Huang, Neiva, & Wang, 2005; G. Pini Prato et al., 2011). Nevertheless, factors such as a limited sample size (common with long-term recall assessments), and/or the singularity of treatment groups among population cohorts may have hindered the assessment of KTW and GT concomitantly as a single entity representing the soft tissue phenotype, or their coexisting relationship to the long-term stability/relapse of the gingival margin. This, set the preface of our current research, which was to obtain a relatively large and homogenous sample aiming to investigate the true nature of this relationship, via a completely data-driven methodology and impartial approach for selection of a statistical model that best explained our gathered longitudinal data.

The merits of such design and analysis include the notion that the analyzed data originate from carefully selected individuals from a homogenous population cohort as they previously participated in RCTs with similar inclusion criteria in the same center. Furthermore, at all follow-up visits, the examinations and data collection were carried out by the same pre-calibrated investigators, in the same manner as was done so in the original trials. Reasonably, these would all lead to substantially reduced unwanted heterogeneity among the sample and eliminate many potential inter-patient and population confounding, increasing the power of our analysis.

Notably, the operators performing the root coverage surgeries and the utilized biomaterials had varied across the six trials. Nevertheless, it can be safely assumed that the effect of the surgeon, or the utilized materials would not exceed any influence on the clinical results beyond the early timepoints, which were not the interest of the current research. Indeed, a plethora of adequately designed RCTs have been published on the short-term efficacy and comparison of root coverage procedures (Cairo, Barootchi, et al., 2020; Cairo, Nieri, & Pagliaro, 2014; Graziani et al., 2014; Tavelli, Barootchi, Cairo, et al., 2019). In fact, in our analysis we noted that the modality of the treatment itself only influenced the early (6-month) outcomes, whereas the subsequent path of the position of the gingival margin, was predominately dependent upon specific-site and local factors, followed by patient-level variations. This indicates that irrespective of the original treatment approach, the outcomes of different root coverage procedures over time (whether presenting with stability or relapse), rely heavily on their ability to modify the constituent of the periodontal soft tissue phenotype, hence through their impact on the components of GT and KTW.

Pini Prato et al. were the first to shed light on the role of KTW on the long-term stability of the gingival margin, following CAF alone, or with a CTG (G. P. Pini Prato, Franceschi, et al., 2018; G. P. Pini Prato, Magnani, et al., 2018). Nevertheless, in these reports, sites had been segregated based on the amount of KTW (to $\geq$2 mm, or $<$ 2 mm), and GT was not assessed. Despite highlighting the importance KTW in these reports, one might speculate that the thickness of the marginal soft tissues may have also contributed to the behavior of the gingival margin and to the recurrence of gingival recessions at these sites. In fact, in the present study, we observed that while GT and KTW can both influence the trajectory of the gingival margin in a similar way (non-linearly, and with diminishing effects), they are weakly correlated and can be largely independent. Hence, in a clinical scenario, either of these soft tissue attributes can be present or absent at any site or coexist with varying degrees. In addition, we observed that among the two components in our dataset, GT appeared as the dominant phenotypic variable that predicted the long-term path of the gingival margin.

Interestingly, despite KTW has long been considered to play a beneficial role on the maintenance of a stable and healthy periodontium (Lang & Loe, 1972; Zucchelli & Mounssif, 2015), the part of GT on root coverage outcomes and on the behavior of the gingival margin over time has only been recently emphasized (Barootchi, Tavelli, Di Gianfilippo, et al., 2021; Barootchi et al., 2020; Rebele, Zuhr, Schneider, Jung, & Hurzeler, 2014; Zuhr et al., 2021). In a recent study, Zuhr and colleagues analyzed the 5-year outcomes of 18 patients that underwent a root coverage procedure as part of a RCT comparing TUN either with CTG or EMD (Zuhr et al., 2021). Despite observing a certain amount of relapse in the gingival margin in both groups, the authors found a significant correlation between volumetrically assessed marginal soft tissue thickness (GT) and Rec reduction at all sites, as well as a correlation between GT and the percentage of root coverage for the CTG-treated group, whereas no analysis of, or a correlation with KTW was reported. In addition, the authors concluded that an increased post-operative GT would lead to less relapse of the gingival margin at 5 years, as well as an increased esthetic outcome (Zuhr et al., 2021).

Similarly in our longitudinal analysis, despite variations in the original treatments among the 157 analyzed treated sites, we found that GT at 6 months prevailed as the dominant soft tissue phenotypic component that predicts the behavior of the gingival margin, with KTW having limited or no effect on the outcome's stability when GT is accounted for. Nevertheless, an important aspect to bear in mind is that all sites at baseline, and at 6 months presented with at least 1.5 mm of KTW. Therefore, the long-term behavior of the gingival margin in case of a complete absence, or minimal presence of KTW can only be speculated. Indeed, studies have suggested that the presence of a band of KTW can facilitate patient oral hygiene, protect from traumatic brushing habits, and reduce the risk for soft tissue relapse (G. P. Pini Prato, Magnani, et al., 2018; Stefanini, Zucchelli, Marzadori, & de Sanctis, 2018; Tavelli, Barootchi, Cairo, et al., 2019; Tavelli, Barootchi, Di Gianfilippo, et al., 2019). Furthermore, drawing conclusion from the landmark study by Lang and Löe in 1972 (Lang & Loe, 1972), many have suggested that an adequate band of KTW – defined as at least 2 mm – is needed for maintaining the stability of the surgical results, a concept which has rather arbitrarily been translated into the field of root coverage, without exploring the exact required or sufficient amount.

In line with recent literature on the overall importance of GT (Barootchi et al., 2020; Cairo, Cortellini, et al., 2020; Zuhr et al., 2020), our findings also corroborate the use of grafting materials, such as xenogeneic collagen or acellular dermal matrices, for the treatment of gingival recessions (Meza-Mauricio et al., 2021; Stefanini et al., 2020; Suzuki et al., 2020). While augmentation of KTW is a prerogative of autogenous grafts, there is no doubt that graft substitutes can provide a significant increase in GT (Rotundo, Genzano, Patel, D'Aiuto, & Nieri, 2019; Tavelli, McGuire, et al., 2020; Tonetti et al., 2018; Zucchelli et al., 2020), which we noted to be qualitatively unchanged over time, in line with a previous systematic review (Barootchi et al., 2020). And adding a soft tissue graft to increase GT may have the potential to reduce the relapse of the gingival margin that have been commonly observed at sites treated with CAF alone (Barootchi et al., 2019a; G. P. Pini Prato, Magnani, et al., 2018; Pini-Prato et al., 2010). Thus, the choice of a soft tissue grafting material for the treatment of GRs should be tailored individually, and upon the initial characteristics of the defect, bearing in mind that aside from a complete root coverage, an early (6-month) post-treatment GT of at least 1.46 mm (or a clinically measurable amount of 1.5 mm) should also be set as a goal of the intervention.

Among the limitations of the current study, the absence of an intermediate time point needs to be acknowledged, as well as the previously stated lack of data in the lower spectrum of KTW for exploring its absolute indication and/or importance, in case of complete absence or bear minimal existence of KTW. It should also be noted that slight discrepancies existed among the original trials for measuring GT, such that the study of Trabulsi et al. 2004, had utilized a penetrating probe, instead of a penetrating endodontic needle for obtaining GT measurements (Trabulsi et al., 2004), and the studies of Wang et al. 2014, and Huang et al. 2005 obtained GT measurements at 1- and 2-mm reference points below the gingival margin, respectively (Huang, Neiva, Soehren, et al., 2005; Wang et al., 2014) (as opposed to the remaining measurements of GT derived from a reference point of 1.5 mm apical to the gingival margin).

As inherent to the nature of long-term follow-up recalls, we also observed a substantial attrition rate in this study. It should also be noted that all available participants at this recall had received at least once yearly professional cleaning. Since we observed that the trajectory of the gingival margin is mainly site-, and then patient-specific, the specific role of oral hygiene care and the impact of its re-instruction could not be explored. This is also due to the unavailability of the measurements of plaque index at all intervals. This may in fact, bear a selection bias due to the presence of only "compliant" individuals at the long-term recall, which despite the benefit of reduced heterogeneity and less possibility for confounding, also limits the generalizability of our findings. As such, the notion that all patients were from the same center – increasing homogeneity and power – may inadvertently also lead to less generalizable results. Therefore, we encourage studies among different population cohorts to corroborate our findings. Nonetheless, as the primary aim of this investigation was to determine possible risk factors, and the influence of site-specific phenotypic variables on the behavior of the gingival margin, a homogenous population cohort that varied mainly with respect to local site-specific factors would best serve the objective of this report.

5. Conclusion

Within the limitations of this study, we conclude that gingival phenotype modification at the short-term predicts the long-term stability of the gingival margin over 10 years. In the presence of at least 1.5 mm of keratinized tissue width, achieving a gingival thickness of 1.46 mm at 6 months after a root coverage procedure was the key determining site characteristic for a stable gingival margin long-term.

Conflict of interest

The authors do not have any financial interests, either directly or indirectly, in the products or information enclosed in the paper. The study was self-supported.

Tables and figures.

Table 1. Descriptive summaries of the clinical outcomes per study treatment at baseline (prior to surgical root coverage), and their corresponding measurements at the early, and long-term follow-up recall.

Table 2. The outcomes of mean and complete root coverage for the included studies and treatment arms.

Table 3. Results of the final model for the analysis of the trajectory of Rec over time.

Figure 1. The flow chart of this study.

Figure 2. The estimated relationship between 10-year change in the level of the gingival margin (recession, Rec), and gingival thickness (GT) at 6 months based on the model.

Table 1. Descriptive summaries of the clinical outcomes per study treatment at baseline (prior to surgical root coverage), and their corresponding measurements at the early, and long-term follow-up recall. Note that the presented data only pertains to patients available at the terminal follow-up recall.

Study/publication	Treatment arm	Average follow-up time point (months)	Rec (mean ± SD) (mm)	KTW (mean ± SD) (mm)	GT (mean ± SD) (mm)
(Byun et al., 2009)/ (Barootchi et al., 2019b)	CAF	0	1.93 ± 1.14	1.68 ± 0.72	1.07 ± 0.37
	CAF	6	0.28 ± 0.42	2.17 ± 0.84	1.25 ± 0.32
	CAF	144	0.82 ± 0.63	2.82 ± 0.66	0.93 ± 0.26
	CAF + eCTG	0	2.54 ± 0.69	2.07 ± 0.67	1.05 ± 0.29
	CAF + eCTG	6	0.11 ± 0.41	3.84 ± 0.55	2.07 ± 0.61
	CAF + eCTG	144	0.57 ± 0.44	3.94 ± 0.54	2.11 ± 0.61
	CAF + CTG	0	2.75 ± 0.85	1.18 ± 0.44	0.9 ± 0.27
	CAF + CTG	6	0.25 ± 0.36	2.62 ± 0.78	1.72 ± 0.29
	CAF + CTG	144	0.62 ± 0.46	3.87 ± 0.69	1.62 ± 0.67
(Huang, Neiva, Soehren, et al., 2005)	CAF	0	2.78 ± 0.53	2.63 ± 1.22	1.18 ± 0.44
	CAF	6	0.5 ± 0.44	3.11 ± 0.62	1.34 ± 0.27
	CAF	216	1.09 ± 0.69	3.45 ± 0.52	1.29 ± 0.21
	CAF + PRP	0	2.96 ± 0.41	2.67 ± 0.42	1.11 ± 0.29
	CAF + PRP	6	0.5 ± 0.39	3.31 ± 0.62	1.39 ± 0.24
	CAF + PRP	216	0.97± 0.99	3.82 ± 0.49	1.33 ± 0.29
(Kimble et al., 2004)	GTR	0	3.02 ± 0.74	1.72 ± 0.85	1.07 ± 0.25
	GTR	6	0.91 ± 0.58	2.21 ± 1.12	1.12 ± 0.37
	GTR	216	1.13 ± 0.89	3.14 ± 0.92	1.15 ± 0.31
Modarressi et al. 2006/ (Tavelli, Barootchi, Di Gianfilippo, et al., 2019)	CAF + FDADM	0	2.56 ± 1.4	3.09 ± 1.27	1.06 ± 0.45
	CAF + FDADM	6	0.41 ± 0.58	2.89 ± 1.12	1.46 ± 0.69
	CAF + FDADM	144	0.84 ± 0.57	3.39 ± 0.89	1.28 ± 0.53
	TUN + FDADM	0	2.29 ± 0.96	2.54 ± 1.16	1.15 ± 0.34

	TUN + FDADM	6	0.31 ± 0.57	2.01 ± 0.69	1.51 ± 0.61
	TUN + FDADM	144	0.91 ± 0.55	2.62 ± 1.57	1.34 ± 0.47
(Trabulsi et al., 2004)	GTR	0	3.11 ± 0.59	3.25 ± 1.89	1.11 ± 0.19
		6	0.82 ± 0.81	3.48 ± 1.64	1.07 ± 0.11
		216	1.01 ± 0.69	4.02 ± 1.19	1.13 ± 0.24
	GTR + EMD	0	3.29 ± 0.62	3.31 ± 1.95	1.03 ± 0.59
		6	1.15 ± 0.65	3.24 ± 1.62	1.02 ± 0.23
		216	1.2 ± 0.8	3.96 ± 1.45	1.08 ± 0.40
(Wang et al., 2014)/(Barootchi, Tavelli, Gianfilippo, et al., 2021)	CAF + FDADM	0	2.5 ± 0.5	2.35 ± 0.55	1.42 ± 0.53
		6	0.64 ± 0.74	2.35 ± 0.74	1.64 ± 0.62
		12	0.57 ± 0.6	2.42 ± 0.61	1.78 ± 0.48
		108	1 ± 0.86	3.07 ± 0.78	1.98 ± 0.53
	CAF + SDADM	0	2.6 ± 0.54	1.9 ± 0.74	1.2 ± 0.27
		6	0.8 ± 1.09	2.1 ± 0.89	1.8 ± 0.27
		12	0.6 ± 0.65	2.4 ± 0.65	1.8 ± 0.27
		108	0.9 ± 0.89	3.2 ± 0.44	1.8 ± 0.27

ADM: acellular dermal matrix. CAF: coronally advanced flap. CEJ: cemento-enamel junction. CTG: connective tissue graft. eCTG: connective tissue graft with an epithelial collar. EMD: enamel matrix derivative. FDADM: freeze-dried acellular dermal matrix. GTR: guided tissue regeneration. MGJ: mucogingival junction. PRP: platelet-rich plasma. SDADM: solvent-dehydrated acellular dermal matrix. TUN: tunnel technique.

Rec, recession; KTW, keratinized tissue width; GT, gingival thickness; mm, millimeter

Table 2. The outcomes of mean and complete root coverage for the included studies and treatment arms. Note that the presented data only pertains to patients available at the terminal follow-up recall.

Study/publication	Treatment arm	Average follow-up time point (months)	mRC (mean ± SD) (%)	CRC (%)
(Byun et al., 2009)/ (Barootchi et al., 2019b)	CAF	6	89.3 ± 16.9	71.4
		144	55.2 ± 32.6	42.9
	CAF + eCTG	6	97.1 ± 10.4	84.6
		144	77.7 ± 18.3	61.5
	CAF + CTG	6	91.0 ± 14.5	81.3
		144	74.5 ± 25.1	56.3
(Huang, Neiva, Soehren, et al., 2005)	CAF	6	81.4 ± 19.9	62.5
		216	60.8 ±18.2	37.5
	CAF + PRP	6	82.2 ± 27.4	57.1
		216	67.2 ± 17.8	28.6
(Kimble et al., 2004)	GTR	6	69.2 ± 14.2	50.0
		216	54.6 ± 18.3	25.0
Modarressi et al. 2006/ (Tavelli, Barootchi, Di Gianfilippo, et al., 2019)	CAF + FDADM	6	88.1 ± 16.9	52.6
		144	65.8 ± 21.7	27.3
	TUN + FDADM	6	89.1 ± 15.2	51.2
		144	63.6 ± 23.4	29.4
(Trabulsi et al., 2004)	GTR	6	70.1 ± 24.3	33.3
		216	61.2 ± 22.2	16.7
	GTR + EMD	6	65.19 ± 21.42	16.7
		216	61.53 ± 27.4	16.7
(Wang et al., 2014)/(Barootchi, Tavelli, Gianfilippo, et al., 2021)	CAF + FDADM	6	74.28 ± 30.71	42.8
		12	75.95 ± 25.12	42.8
		108	58.8 ± 38.2	28.5
	CAF + SDADM	6	73.3 ± 36.51	60.0
		12	78.8 ± 21.73	40.0
		108	66.6 ± 31.2	40.0

ADM: acellular dermal matrix. CAF: coronally advanced flap. CRC: complete root coverage. CTG: connective tissue graft. eCTG: connective tissue graft with an epithelial collar. EMD: enamel matrix derivative. FDADM: freeze-dried acellular dermal matrix. GTR: guided tissue regeneration. mRC: mean root coverage. PRP: platelet-rich plasma. SDADM: solvent-dehydrated acellular dermal matrix. TUN: tunnel technique.

Table 3. Results of the final model for the analysis of the trajectory of recession (Rec) over time.

Fixed-effect parameters

	Estimate	Std. Error	95% CI (LB, UB)	*p* value
Time*	0.06	0.003	0.05, 0.07	<0.001
6-month GT#	0.07	0.09	-0.08, 0.23	0.28
6-month GT time interaction*	-0.06	0.006	-0.07, -0.04	<0.001
Initial recession	0.22	0.03	0.15, 0.29	<0.001

Random-effect parameters

	Standard deviation
Site/tooth	0.327
Patient	0.151
Treatment type	0.091
Study	0.193
Study time slope per year	0.027
Residual	0.249

Note that results of the fixed-effect parameters are expressed according to each parameter. Model random effects are expressed in the units of millimeters.
* Time is in years
# Power-transformed gingival thickness at 6 months
CI, confidence intervals; LB, lower bound, UB, upper bound

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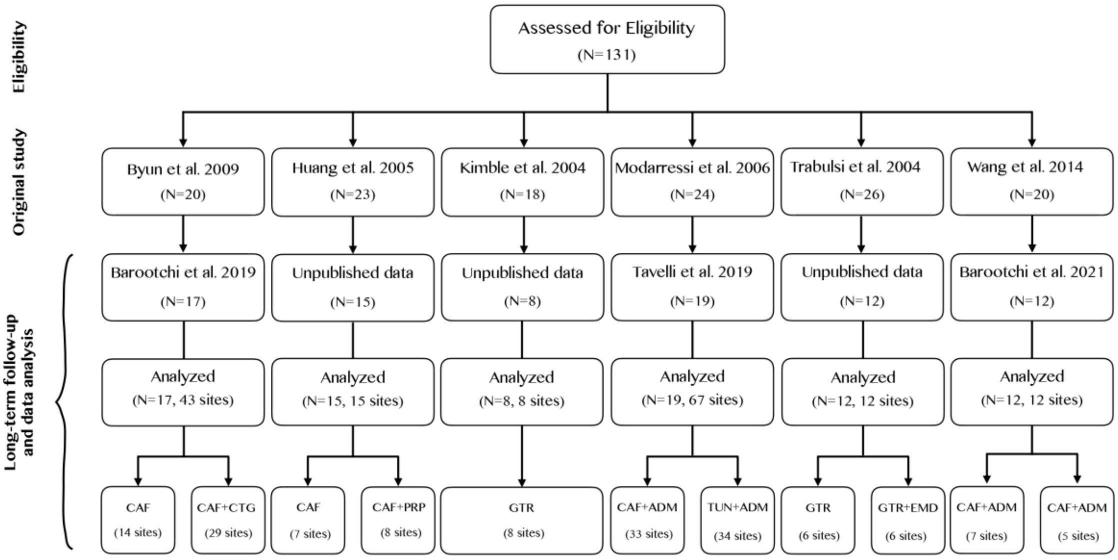
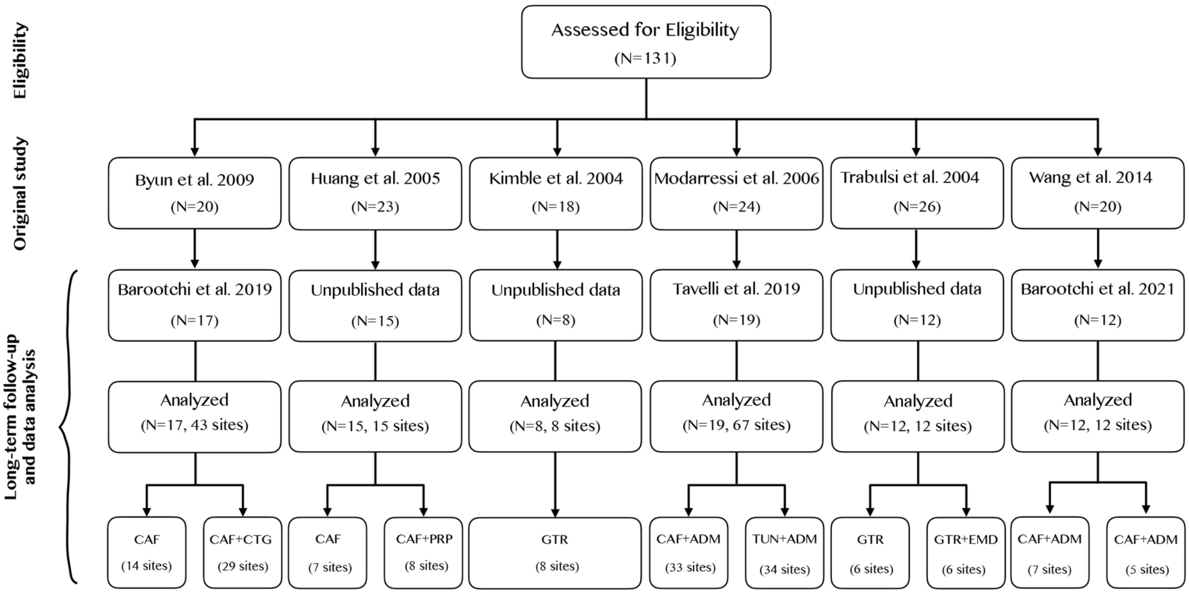

Eligibility
Assessed for Eligibility
(N=131)
Original study
Byun et al. 2009
(N=20)
Huang et al. 2005
(N=23)
Kimble et al. 2004
(N=18)
Modarressi et al. 2006
(N=24)
Trabulsi et al. 2004
(N=26)
Wang et al. 2014
(N=20)
Long-term follow-up and data analysis
Barootchi et al. 2019
(N=17)
Unpublished data
(N=15)
Unpublished data
(N=8)
Tavelli et al. 2019
(N=19)
Unpublished data
(N=12)
Barootchi et al. 2021
(N=12)
Analyzed
(N=17, 43 sites)
Analyzed
(N=15, 15 sites)
Analyzed
(N=8, 8 sites)
Analyzed
(N=19, 67 sites)
Analyzed
(N=12, 12 sites)
Analyzed
(N=12, 12 sites)
CAF
(14 sites)
CAF+CTG
(29 sites)
CAF
(7 sites)
CAF+PRP
(8 sites)
GTR
(8 sites)
CAF+ADM
(33 sites)
TUN+ADM
(34 sites)
GTR
(6 sites)
GTR+EMD
(6 sites)
CAF+ADM
(7 sites)
CAF+ADM
(5 sites)



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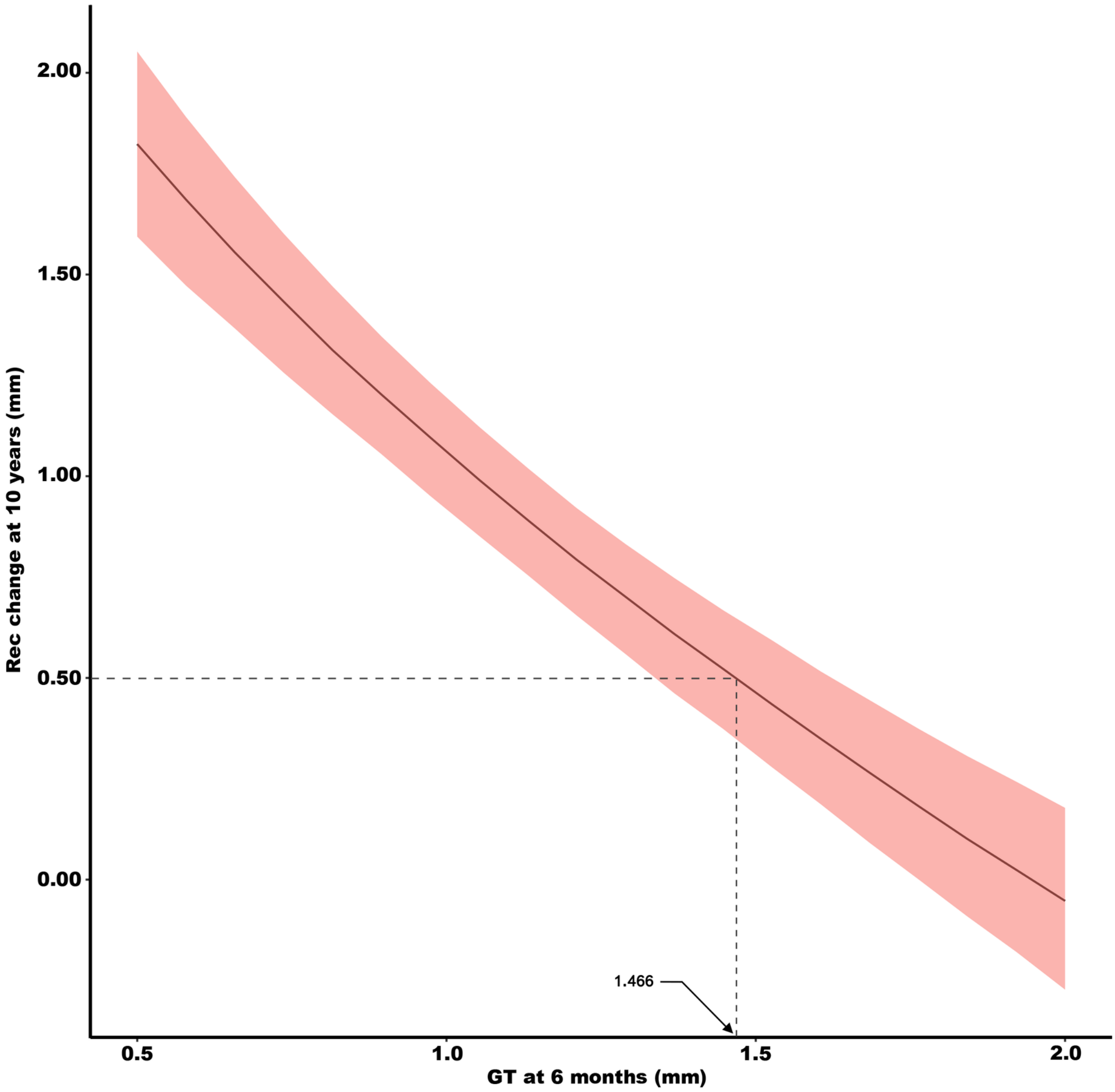

JCPE_13641_Figure 2.tif