

ORIGINAL ARTICLE

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) behaviour 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, 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.

KEYWORDS

evidence-based dentistry, gingival recession, periodontitis, root coverage, soft tissue augmentation

Clinical Relevance

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

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Principal findings: Soft tissue phenotype modification following a root coverage procedure influences the long-term behaviour 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, achieving 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

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

Recently, the long-term behaviour of the gingival margin after root coverage procedures as well as the outcomes of the initial therapies overtime have been studied (Barootchi et al., 2019; Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Petsos et al., 2020; 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 et al., 2020; Kao et al., 2020; Kim et al., 2020).

It has been suggested that sites with a thin, soft tissue phenotype are more prone to developing gingival recessions (or its re-occurrence) (Scheyer et al., 2015; Cortellini & Bissada, 2018) and that their modification may increase tolerance against some of the aetiological factors of gingival recessions, such as resuming traumatic toothbrushing habits in non-compliant individuals (Chambrone & Tatakis, 2015; Chambrone et al., 2019; Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Barootchi et al., 2020). 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 (Pini Prato, Magnani, & Chambrone, 2018; Barootchi et al., 2019; Chambrone et al., 2019; Tavelli, Barootchi, Cairo, et al., 2019). Thus, the combined use of grafting materials to achieve phenotype modification may improve not only early root coverage outcomes but also the long-term results and the maintenance of the gingival margin over time (Chambrone & Tatakis, 2015; Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Barootchi et al., 2020).

Recent studies 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 (Pini Prato, Franceschi, et al., 2018; Rasperini et al., 2018; Barootchi et al., 2019; Tavelli, Barootchi, Cairo, et al., 2019). Despite the significance of these reports, as they relate 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 inter-relationship relative to the long-term behaviour 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) behaviour of the gingival margin.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The present study was designed as a two-point longitudinal observational analysis of previous randomized clinical trials (RCTs) on the treatment of gingival recession (GR) defects, conducted at the Department of Periodontics and Oral Medicine, School of Dentistry, University of Michigan.

From May 2019 to January 2021, participants from six parallel-design RCTs were individually re-contacted and invited for a follow-up visit and clinical re-examination. Details of the original RCTs can be found in their respective reports (Kimble et al., 2004; Trabulsi et al., 2004; Huang, Neiva, Soehren, et al., 2005; Byun et al., 2009; Wang et al., 2014, 2015; Tavelli, Barootchi, Di Gianfilippo, et al., 2019) as well as in Appendix. Individual follow-up reports of three of the six clinical trials can also be found elsewhere (Barootchi et al., 2019; Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Barootchi, Tavelli, Di Gianfilippo, Eber, et al., 2021).

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/>).

2.2 | Original interventions and recruitment criteria

All surgical treatments were 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 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, 2015), or platelet-rich plasma (Huang, Neiva, Soehren, et al., 2005). The tunnelling approach was employed in one trial (Tavelli, Barootchi, Di Gianfilippo, et al., 2019) with either 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 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 et al., 2011) gingival recession defects of depth of at least 2 mm. Details on the eligibility criteria of all trials are given in 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 aetiology of the GRs (more details presented in Appendix).

2.3 | Clinical examination at the long-term recall

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

2.4 | 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 would predict the longitudinal change in the level of the gingival margin at the 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 SD were used to descriptively summarize continuous data. To evaluate early predictors of the longitudinal changes in the gingival margin (Rec) at the treated sites within patients, multilevel linear regression was used, employing a data-driven approach for model construction based on the Akaike information criterion (AIC) (Burnham & Anderson, 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, and 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 unambiguously 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, per 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 modelled as random rather than fixed 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 the relationships between Rec and either GT or KTW, which 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 & Anderson, 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 confirmed associations with gingival margin relapse (Rec). Confidence intervals were produced for fixed effects, and a p -value threshold of .05 was set for statistical significance. The model selection process, along with a complete list of all models and their corresponding AIC values, is shown in 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.

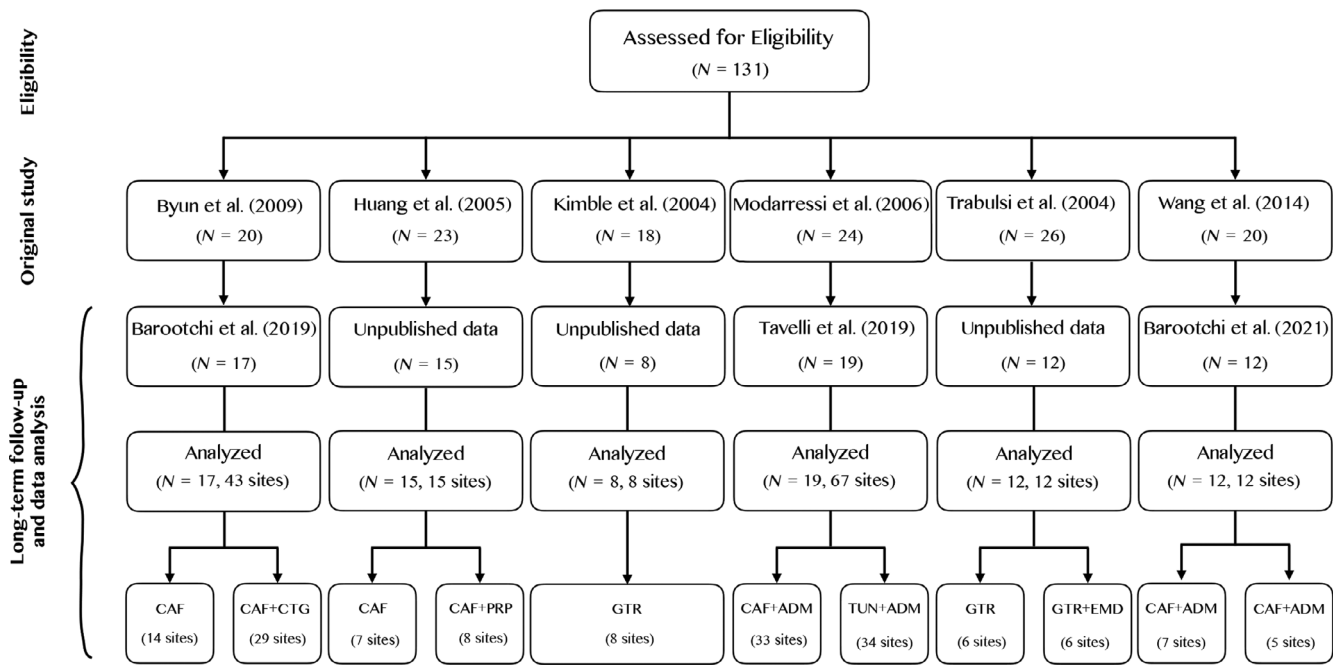


FIGURE 1 Flow chart of this study. ADM, acellular dermal matrix; CAF, coronally advanced flap; CTG, connective tissue graft; EMD, enamel matrix derivative; GTR, guided tissue regeneration; PRP, platelet-rich plasma; TUN, tunnel technique

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 (Shayan Barootchi and Kerby Shedden), and the following R packages were used: tidy (Wickham & Henry, 2019), arm (Gelman & Su, 2020), dplyr (Wickham et al., 2019), lme4 (Bates et al., 2015), merTools (Knowles & Frederick, 2019), ggplot2 (Wickham, 2016), and ggeffects (Lüdtke, 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 (9–18 years post treatment). Figure 1 shows the per-study and per-treatment sample sizes at the follow-up time point. General information on the demographic and clinical characteristics of the samples can also be found in Table S1.

Throughout the follow-up period, all participants received professional oral prophylaxis, hygiene care, and/or supportive periodontal therapy at least once a year (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. Although none of the recruited participants in the original

studies was a smoker, 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 than their levels at 6 months, while the values of GT and PD were nearly 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 Appendix. The best fitting model for explaining the trajectory of Rec throughout time included main effects for time, power-transformed GT at 6 months, and time by 6-month GT interaction (Table 3). In this model, Rec changes linearly over time within subject sites, with the intercept and slope dependent on the 6-month GT value.

GT at 6 months ranged from 0.5 to 2 mm, with larger 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

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

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. (2019)	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, Di Gianfilippo, Eber, 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

Note: The presented data only pertains to patients available at the terminal follow-up recall.

Abbreviations: 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; GT, gingival thickness; GTR, guided tissue regeneration; KTW, keratinized tissue width; MGJ, muco-gingival junction; PRP, platelet-rich plasma; Rec, recession; SDADM, solvent-dehydrated acellular dermal matrix; TUN, tunnel technique.

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 that after adjusting for 6-month GT, KTW no longer had a statistically significant association with Rec (models 2 and 3, Appendix). However,

TABLE 2 Outcomes of mean and complete root coverage for the included studies and treatment arms

Study/publication	Treatment arm	Average follow-up time point (months)	mRC (mean ± SD) (%)	CRC (%)
Byun et al. (2009)/Barootchi et al. (2019)	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, Di Gianfilippo, Eber, 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

Note: The presented data pertains only to patients available at the terminal follow-up recall.

Abbreviations: 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.

when excluding GT from the model, KTW predicted the trajectory of the gingival margin similar 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 larger 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, which 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, although 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 specific to the treatment type.

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 behaviour 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, and

Fixed-effect parameters				
	Estimate	SE	95% CI (LB to UB)	p-Value
Time ^a	0.06	0.003	0.05 to 0.07	<.001
6-month GT ^b	0.07	0.09	-0.08 to 0.23	.28
6-month GT-time interaction ^a	-0.06	0.006	-0.07 to -0.04	<.001
Initial recession	0.22	0.03	0.15 to 0.29	<.001
Random-effect parameters				SD
Site/tooth				0.327
Patient				0.151
Treatment type				0.091
Study				0.193
Study time slope per year				0.027
Residual				0.249

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

Note: Results of the fixed-effect parameters are expressed according to each parameter. Model random effects are expressed in the units of millimetres.

Abbreviations: CI, confidence interval; GT, gingival thickness; LB, lower bound, UB, upper bound.

^aTime is in years.

^bPower-transformed gingival thickness at 6 months.

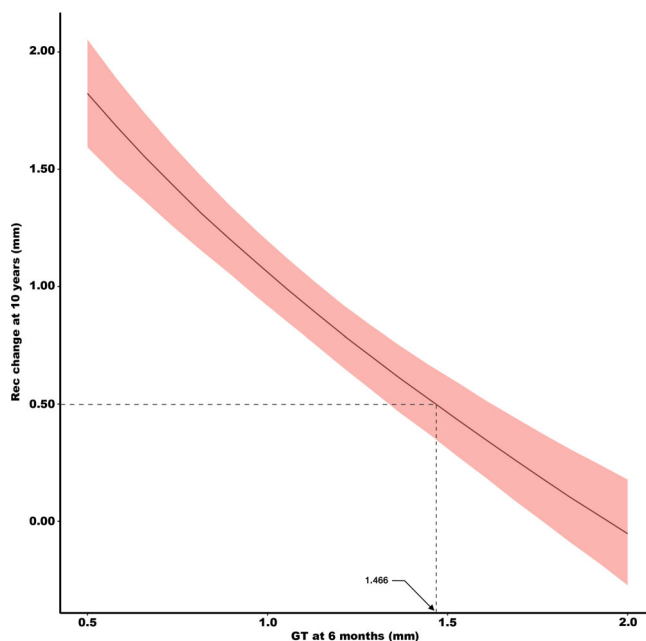


FIGURE 2 Estimated relationship between 10-year change in the level of the gingival margin (recession, Rec), and gingival thickness (GT) at 6 months based on the model

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 has been

expressed extensively throughout the literature (Kennedy et al., 1985; Parma-Benfenati et al., 1985; Stetler & Bissada, 1987; Anderegg et al., 1995; Lin et al., 2013; Perussolo et al., 2018). Also, 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 (Huang, Neiva, & Wang, 2005; Pini Prato et al., 2011; Cairo et al., 2016). 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 analysed data originate from carefully selected individuals from a homogenous population cohort that previously participated in RCTs with similar inclusion criteria in the same centre. 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 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 biomaterials used, had varied across the six trials. Nevertheless, it can be safely assumed that the effect of the surgeon or the used materials would not have any influence on the clinical results beyond the early time points, which were not the interest of the current study. Indeed, a plethora of adequately designed RCTs have been published on the short-term efficacy and comparison of root coverage procedures (Cairo et al., 2014; Graziani et al., 2014; Tavelli, Barootchi, Cairo, et al., 2019; Cairo, Barootchi, et al., 2020). In fact, in our analysis we noted that the modality of the treatment itself influenced only 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 and hence through their impact on the components of GT and KTW.

Pini Prato, Franceschi, et al. (2018) and Pini Prato, Magnani, and Chambrone (2018) 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. Nevertheless, in these reports, sites had been segregated based on the amount of KTW (≥ 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 behaviour of the gingival margin and to the recurrence of gingival recessions at these sites. In fact, in the present study we observed that although both GT and KTW can 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 behaviour of the gingival margin over time has been only recently emphasized (Rebele et al., 2014; Barootchi et al., 2020; Barootchi, Tavelli, Di Gianfilippo, Stefanini, et al., 2021; Zuhr et al., 2021). In a recent study, Zuhr et al. (2021) analysed the 5-year outcomes of 18 patients who underwent a root coverage procedure as part of an RCT comparing TUN either with CTG or EMD. 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 aesthetic outcome (Zuhr et al., 2021).

Similarly, in our longitudinal analysis, despite variations in the original treatments among the 157 analysed treated sites, we found that GT at 6 months prevailed as the dominant soft tissue phenotypic component that predicts the behaviour of the gingival margin, with KTW having only a 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 behaviour 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 (Pini Prato, Magnani, & Chambrone, 2018; Stefanini et al., 2018; Tavelli, Barootchi, Cairo, et al., 2019; Tavelli, Barootchi, Di Gianfilippo, et al., 2019). Furthermore, drawing conclusion from the landmark study by Lang and Loe 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 that 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 (Stefanini et al., 2020; Suzuki et al., 2020; Meza-Mauricio et al., 2021). While augmentation of KTW is a prerogative of autogenous grafts, there is no doubt that graft substitutes can provide a significant increase in GT (Tonetti et al., 2018; Rotundo et al., 2019; Tavelli, McGuire, et al., 2020; 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, which has been commonly observed at sites treated with CAF alone (Pini-Prato et al., 2010; Pini Prato, Magnani, & Chambrone, 2018; Barootchi et al., 2019). 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 Huang, Neiva, Soehren, et al. (2005) and Wang et al. (2014) made 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-specific 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 centre—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 behaviour 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 KTW, achieving a GT of 1.46 mm at 6 months after a root coverage procedure was the key determining site characteristic for a stable gingival margin in the long term.

AUTHOR CONTRIBUTIONS

Shayan Barootchi: Conception and design of the study; served as one of the examiners at the final follow-up, statistical analysis and interpretation of data; initial and final drafting of the work; final approval of the version to be published; accountable for all aspects of the work. **Lorenzo Tavelli:** Contribution to the study design; initial and final drafting of the work; provided all clinical aspects of the work; gave final approval of the version to be published. **Riccardo Di Gianfilippo:** Served as an examiner for the final follow-up visit; manuscript draft; critical review of the manuscript; accountable for all aspects of the work. **Kerby Shedden:** Study design; statistical analysis and interpretation of data; critical review of the manuscript; final review of the work and accountable for all aspects. **Tae-Ju Oh:** Manuscript preparation and the initial draft; final review of the work; accountable for all aspects of the work. **Giulio Rasperini:** Manuscript preparation and the

initial draft; final review of the work; accountable for all aspects of the work. **Rodrigo Neiva:** manuscript preparation and the initial draft; final review of the work; accountable for all aspects of the work. **William V. Giannobile:** Contributed to study design; critical review of manuscript draft; approval of the work and accountable for all aspects. **Hom-Lay Wang:** Contributed to study design; oversight of patient recruitment; calibration; critical review of manuscript draft; approval of the work and accountable for all aspects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICAL STATEMENT

The study was registered and approved by the Western Institutional Review Board (HUM00146261), and was carried out in complete accordance with the Declaration of Helsinki 1975, as revised in 2000. All patients had provided their informed consent.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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