

Dimensional Changes in Free Epithelialized Gingival/Mucosal Grafts at Tooth and Implant Sites: A Prospective Cohort Study

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Abstract

Background: A study was made of the dimensional changes in free epithelialized gingival/mucosal grafts (FEGs) used to augment keratinized tissue (KT) at tooth and implant sites, and of the confounders influencing the dynamic changes over 6 months of follow-up.

Material and methods: A prospective cohort interventional study was made of implant and tooth sites needing keratinized tissue augmentation by means of an apically positioned flap and FEG. Six intraoperative variables were recorded at baseline (T0). In addition, graft width (GW), graft length (GL) and graft dimension (GD) were assessed at three weeks (T1), three months (T2) and 6 months of follow-up (T3). Univariate and multivariate analyses were performed to explore associations between the demographic and intraoperative variables and the outcomes over the study period.

Results: Based upon an *a priori* power sample size calculation, a total of 56 consecutive patients were recruited, of which 52 were available for assessment. A total of 73 graft units were included in 122 sites. At T3, the mean change in GD in FEG was 40.21%. In particular, the mean changes in GL and GW were 12.13% and 33.06%, respectively. Statistically significant changes in GD were recorded from T0 to T1 ($p < 0.0005$) and from T1 to T2 ($p < 0.0005$), but not from T2 to T3 ($p = 0.13$). The change in GD at T3 was 33.26% at tooth and 43.11% at implant site level ($p = 0.01$). Age and GW assessed at T0 proved to be related to the changes in GD and GW in the univariate and multivariate analyses. The univariate analysis showed the avascular area (AA) to be related to the changes in GD and GW at the implant sites, while graft thickness (GT) was associated to changes in GD and GW at the tooth sites in the univariate and multivariate analyses.

Conclusions: Free epithelialized grafts are exposed to dimensional changes that result in a reduction of approximately 40% of the original graft dimension - the changes being approximately 10% greater at the implant sites than at the tooth sites (NCT04410614).

Introduction

Soft tissue characteristics at tooth and implant sites were a subject of debate for decades, in particular as regards the significance of keratinized gingiva/mucosa in relation to periodontal/peri-implant health.¹⁻⁶ Later findings, however, suggested that the presence of keratinized tissue (KT) at tooth and implant sites affords greater stability of the gingival/mucosal margin, and is associated to less clinical inflammation.⁶⁻⁸ This was found to be more evident at implant sites compared to the contralateral tooth sites.⁹ In turn, clinical studies demonstrated that the proinflammatory profile, defined by inflammatory mediators and cytokines such as prostaglandin E2 (PgE2),¹⁰ tumor necrosis factor- α (TNF- α)¹¹ and interleukin 1- β (IL-1 β),¹¹ is upregulated at implant sites that exhibit < 2 mm of keratinized mucosa (KM). Therefore, interventions seeking to gain KT at tooth and implant sites in areas characterized by a mobile mucosa have been advocated for the prevention and management of periodontal and peri-implant disorders.^{12,13}

The use of apically positioned flaps (APFs) combined with free epithelialized gingival/mucosal grafts (FEGs) were suggested to predictably modify the periodontal/peri-implant soft tissue phenotypes with the aim of augmenting KT and promoting long-term health.^{13,14} It should be noted that these strategies have shown less favorable outcomes in terms of aesthetics (i.e., color match)¹⁵ when compared to other interventions such as coronally advanced flaps in combination with other grafting approaches such as de-epithelialized grafts.¹⁶ Furthermore, one of the notorious shortcomings associated with this technique is graft dimensional changes, which can eventually compromise the desired final outcome.¹⁷

Sullivan and Atkins reported that autograft shrinkage occurred at two main timepoints, namely immediately after harvesting and during the healing process.¹⁸ In particular, thicker grafts tend to exhibit greater immediate contraction upon detachment from the donor zone, due to their greater elastic fiber content, though with less secondary contraction during the healing period, and demonstrate greater resistance to functional stresses. Contrarily, thinner grafts can be more easily maintained through diffusion, and neovascularization is easier to achieve – though such grafts display greater secondary shrinkage.¹⁹ Furthermore, the nature of the recipient bed,²⁰ the graft stabilization approach employed,²¹ the adjacent gingival phenotype,²² or smoking habit,²³ among other variables,²⁰ have been shown to have an impact upon graft stability during healing. Nonetheless, the role played by intraoperative variables in relation to dimensional changes at tooth and implant sites remains unclear. Thus, the purpose of the present prospective cohort study was to assess the dynamic dimensional changes over 6 months of follow-up when using FEGs simultaneous to APFs at tooth and implant sites with the aim of gaining KT.

Material and Methods

A prospective cohort interventional study was carried out from May 2020 to July 2021 in accordance with the principles of the Declaration of Helsinki, and was approved by the Research Ethics Committee of the *Gerencia del Area de Salud de Badajoz* (Badajoz, Spain). The study was carried out in a private practice (CICOM Monje, Badajoz, Spain). All the interventions and records were conducted by a single periodontist (AM), who also supervised the patients during supportive therapy. This study was registered and approved by www.clinicaltrials.gov (NCT04410614). The study was reported following the items checklist of the STROBE statement.²⁴

Study population

Patients in need of FEG as primary or secondary prevention or management of periodontal and/or peri-implant diseases were recruited. The following inclusion criteria were applied: patients between 18-80 years of age, non-smokers, a lack of or an insufficient (< 2 mm) band of keratinized gingival (KG) or mucosa (KM) at the buccal aspect of teeth/implants, and no presence of systemic diseases or medications known to alter bone or soft tissue metabolism. Patients were further eligible if they exhibited healthy or gingivitis-affected teeth or implants in need of primary prevention (during second stage implant surgery), secondary prevention (due to mucositis defined as profuse bleeding on probing)²⁵ or anti-infectious therapy (due to peri-implantitis).²⁵ The exclusion criteria were: pregnant or breastfeeding women, smokers, or individuals with uncontrolled medical conditions or an unwillingness to undergo the free soft tissue grafting intervention or attend the regular check-ups for monitoring the dimensional changes.

Surgical intervention at tooth sites

A partial thickness (mucosal) flap was raised following the mucogingival margin. Then, the mucosal flap was apically positioned. Root scaling was performed before the graft was stabilized, using Gracey curettes*.

Surgical intervention at implant sites

For procedures seeking to augment KM during second stage implant surgery, no intervention other than placing the healing abutments was carried out simultaneous to APF and FEG. In

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contrast, for the management of peri-implantitis, APF, implantoplasty[†] and osteoplasty at the crestal aspect (if needed) were carried out as part of anti-infectious therapy.

Free epithelialized gingival/mucosal grafting description

The FEG were harvested from the palate. The extent was calculated according to the length and width estimated using a 15C blade[‡]. Graft thickness varied, though attempts were made to secure a thickness of about 1.5 mm (including epithelium and lamina propria). The graft was then soaked in saline solution and sutured using simple interrupted Nylon 5.0 or 6.0[§] and Vycril 5.0^{**} sutures upon the recipient bed. If needed, periosteal cross mattress sutures were used. Surgical cyanoacrylate^{††} was then applied to protect the donor wound. Resorbable polyglactin 910 4.0 cross sutures^{‡‡} were placed on top, and an acrylic suck-down device was customized for each patient.

Demographic variables

The recorded demographic variables included age, gender, tooth/implant site (anterior and posterior) and the type of intervention involved (periodontal soft tissue augmentation/peri-implant soft tissue augmentation).

Intraoperative variables

[†] Meisinger LLC, Nauss, Germany

[‡] Swann-Morton, Sheffield, England

[§] Resorba[®] Sutures, Osteogenics Biomedical, Lubbock, TX, USA

^{**} Vycril[®], Ethicon Inc, New Jersey, USA

^{††} Peryacril[®] 90HV, Glustitch Inc, Delta, Canada

^{‡‡} Vycril[®], Ethicon Inc, New Jersey, USA

The following site-specific variables were recorded at the zenith of the implant/tooth site (Figure 1):

- Avascular area (AA): the area (in mm²) of the bone dehiscence at the tooth or implant in close contact with the graft. The area was determined examining the width and length of the avascular bed using a North Carolina Probe.
- Recipient bed thickness (RBT): the thickness (in mm) of the vascular recipient bed determined using a North Carolina Probe approximately 3 mm below the mucosal zenith.
- Graft length (GL): the length (in mm) of the graft measured using a North Carolina Probe.
- Graft width (GW): the width (in mm) of the graft measured using a North Carolina Probe.
- Graft dimension (GD): the dimension (in mm²) of the graft determined examining the graft length and width.
- Graft thickness (GT): the mean thickness (in mm) of the soft tissue graft measured using calipers. The mean value was calculated from three measurements along the graft.

Clinical variables during the study period

These data have been included within the text. The following clinical parameters were recorded at the 3-week (T1), 3-month (T2) and 6-month postoperative recall visits (T3): GL, GW and GD.

In the event the newly-formed gingiva/mucosa could not be identified, Lugol staining was used to outline the area.²⁶

Postoperative care

The patients were instructed to apply an antimicrobial gel in the area three times a day during two weeks (Lacer MucoRepair®, Lacer, Barcelona, Spain), and systemic amoxicillin (750 mg, 2 tablets per day during 7 days) and antiinflammatory medication (Ibuprofen, 600 mg, 1 tablet every 6 hours during 5 days) were also prescribed. The sutures were removed after 2-3 weeks, and the patients were advised to resume oral hygiene.

Statistical analysis

An *a priori* power analysis was carried out for sample size calculation, based on a study published elsewhere,²³ in order to establish statistical significance ($p < 0.05$). Assuming a standard deviation of 1 mm, a minimum clinical difference of 0.75 mm, a ratio between implant and tooth of 2, an alpha error and beta error of 0.05 and 0.20, respectively, and a dropout rate of 15%, a total of 50 and 25 graft units were found to be needed in the implant sites and tooth sites group, respectively. Quantitative variables were reported as the mean and standard deviation (SD), while frequencies and percentages were used to describe qualitative variables. Differences between groups were evaluated using the chi-squared test or Fisher's exact test (if at least one cell was ≤ 5) for categorical variables and the student t-test or equivalent nonparametric tests (Mann-Whitney U-test or Wilcoxon test) for quantitative variables, after assessing the normality of data distribution with the Shapiro-Wilk test. In order to test possible predictors of GW reduction, a univariate analysis was performed employing a three-level (patient, graft, implant/tooth) random intercept linear mixed model, using percentage GW reduction as dependant variable and age, gender, intervention, GT, RBT, AA, GL, GW, tooth/implant position and type of site (tooth versus implant) as independent variables. Subsequently, only those variables that exhibited $p < 0.20$ were entered in the multivariate analysis, which was carried out employing a stepwise three-level random intercept linear mixed model. Likewise, univariate and multivariate analyses were conducted

for both the tooth and implant subgroups. The SPSS version 26 statistical package (Armonk, New York, USA) was used throughout. Statistical significance was considered for $p < 0.05$.

A Cohen intra-examiner agreement rate was calculated to test the accuracy of the examiner during assessment of the clinical variables in the course of the study period. As part of training, GW and GL were assessed at two different timepoints (before and after supportive maintenance therapy). The study was started when the examiner reached $> 85\%$ agreement in a representative sample of 12 patients (20% of the sample size).

Results

Demographic data

A total of 56 consecutive patients ($n_{\text{teeth}} = 22$; $n_{\text{implants}} = 34$) were recruited. Of these, four dropped out during the study period ($n_{\text{teeth}} = 1$; $n_{\text{implants}} = 3$). Of the patients eligible for analysis, 82.1% were females, and the mean age was 52.4 ± 14.6 year. A total of 73 graft units at 122 sites were included. Anterior mandibular sites predominated over other sites (34.9%). None of the intraoperative variables yielded statistical significance at T0, except AA ($p < 0.0005$) favoring implant compared to tooth sites (Supplementary Table 1). A Cohen intra-examiner agreement rate of 100% and 92% was reached for GW and GL, respectively before the initiation of the study.

Free epithelialized gingival/mucosal graft dimensional changes

At the 6-month follow-up assessment (T3), the mean change in GD was 40.21%. In particular, the mean GL and GW reductions were 12.13% and 33.06%, respectively, at T3. Similar dimensional changes were reported at T1 when compared to T0 (16.32%) and at T1 compared to T2 (15.31%). This yielded statistical significance at both timepoints ($p < 0.0005$). Only minor changes occurred from T2 to T3 (1.8%), without reaching statistical significance

($p=0.13$). The mean difference in GD between the tooth and implant sites was statistically significant at T3 ($p=0.01$). In particular, the decrease in GD at T3 was 33.26% at the tooth sites and 43.11% at the implant sites. A similar tendency was noted for the tooth and implant sites in the course of the study period, becoming more notorious at T2, since GW and GD at the implant sites yielded greater statistical significance ($p<0.0005$) compared to the tooth sites ($p=0.004$) (Table 1, Figures 2 and 3 and Supplementary Table 2).

Confounders of free epithelialized gingival/mucosal graft dimensional changes

The univariate and multivariate analyses yielded statistical significance between GD and GW and age ($p=0.002$) and GW assessed at T0 ($p<0.0005$). Moreover, the type of intervention simultaneous to soft tissue grafting further demonstrated significance in the univariate analysis. In particular, FEG when performed simultaneous to peri-implantitis anti-infectious therapy showed significantly more dimensional changes when compared to other interventions to augment KG/KM at the tooth and implant sites ($p=0.002$). On evaluating the tooth sites independently, GT furthermore showed significance in the univariate ($p=0.003$) and multivariate analyses ($p=0.009$). For the implant sites, AA exhibited statistical significance in the univariate analysis ($p=0.01$) (Table 2).

Discussion

Principal findings

The findings from this prospective cohort study showed that: (1) FEGs are exposed to dimensional changes that result in a reduction of approximately 40% of the original GD; (2) the GD changes are essentially attributable to a decrease in GW, which was approximately 70% compared to GL; (3) the FEG dimensional changes were about 10% greater at the implant sites than at the tooth sites; (4) wider FEGs in older patients are prone to exhibit

greater dimensional changes; (5) thicker grafts are more consistent with graft stability at tooth sites; and (6) FEGs stabilized in areas with greater AA are exposed to greater GD and GW changes at implant sites. The later finding may reflect the fact that GD and GW were significantly greater when FEGs were performed simultaneous to anti-infectious therapy, where the AA of the implant is greater.

Agreements and discrepancies with previous findings

The use of FEGs has been advocated to gain attached tissue,²⁷ deepening the vestibule,²⁸ and also to attempt root coverage.²⁹ The technique was originally described in the 1960s by several authors.^{18,30,31} Since then, clinical studies have sought to understand the factors influencing graft integration/success^{20,32,33} and dimensional stability.^{17,20,22,23} Sullivan and Atkins showed capillary outgrowths to be crucial in the development of granulation tissue and in the vascularization of FEGs.¹⁸ As such, graft areas outlined by a denuded root/implant surface or cortical bone may suffer necrosis.

In addition, the literature has shown the following elements and strategies to be crucial in reducing GD changes: (1) FEGs used to gain KM at implant sites in contrast to grafts used to augment KG at tooth sites;¹⁷ (2) intermediate thickness grafts when compared to very thin grafts;²⁰ (3) grafts in non-smokers compared to smokers;²³ (4) the presence of a thick gingival phenotype and KT at adjacent sites compared to thin phenotypes;²² and (5) stabilization using cyanoacrylate compared to suturing up.²¹ The present study further contributes to understanding of the variables that dictate graft stability. For instance, it was seen that for tooth and implant sites, GW is pivotal in predicting GD and GW changes. In the light of our findings, it is speculated that wider grafts have been used in scenarios where the vestibule is shallower, and thus more collapse of the mucogingival or alveolar mucosal junction is anticipated rather than “shrinkage” of the graft. In this sense, we feel that this term is

inaccurate, considering that GW and GL were not seen to undergo dimensional changes of proportional magnitudes. These changes thus occur as a consequence of vertical collapse, rather than of "shrinkage" attributable to factors inherent to the properties of the FEG or to the nature of the recipient site. This phenomenon has also been described elsewhere.^{17,34} Furthermore, it can be speculated that implant sites may have a shallower vestibule due to alveolar ridge atrophy after tooth extraction than that found at tooth sites.³⁵ This may partially explain the difference in changes in GD and GW.

Not surprisingly, thicker grafts were seen to experience lesser dimensional changes at tooth sites. This is in agreement with previous studies²⁰ that reported an average difference of approximately 15% between very thin (GT 0.3 mm) and scalpel-thick grafts (GT 0.9 mm). It has been hypothesized that the stability of thicker grafts is linked to resistance to functional stresses.¹⁸ Interestingly, the univariate analysis showed AA to be associated to dimensional changes at implant sites. This finding was not surprising, given that in avascular zones, there are no capillary outgrowths to promote plasma circulation and organic binding.³⁶ Hence, it is worth noting that whenever soft tissue grafting is performed at implant sites to increase the KM band - in particular simultaneous to anti-infectious therapy for the management of peri-implantitis - the graft must be secured within the vascular recipient bed, and no attempt should be made to coronally reposition the mucosal margin with the aim of covering the recession, since this may result in partial necrosis of the FEG.

Graft dimensional changes have been more extensively documented at tooth sites than at implant sites. At tooth sites, changes ranging from 25% to 48.3% have been reported.^{20,34,37,38} Thus, our findings are in line with the data found in the literature. At implant sites, the reported mean GD changes range from 33% to 61.8%.^{17,26,39,40} In fact, a comparative study showed that after 12 months of follow-up, the mean GD changes were two-fold greater at implant (61%) compared to tooth sites (36%).¹⁷ This is in partial agreement with our own findings.

Nevertheless, it must be noted that the difference in terms of GD changes at the tooth and implant sites favored the latter by only about 10%. The differences between outcomes might be attributable to differences in operator expertise, considering that the interventions in the present study were performed by a specialist, in contrast to trainees in a university setting. It is speculated that the grafts were stabilized over the implant/superstructure. That portion of the graft associated with the AA ("dead space")³⁶ was more likely to slough off - leading to more GD changes. In addition, it should be noted that the residual periodontal ligament may contribute through the formation of granulation tissue, favoring a smoother revascularization phase.⁴¹

Limitations and recommendations for future research

The shortcomings inherent to the study design must be mentioned. Firstly, clinical measurements were carried out with a periodontal probe; errors derived from this approach are therefore likely. To overcome this limitation, it is advisable for future studies to assess GD changes using three-dimensional scanning devices. Furthermore, given that GW experienced substantially more changes than GL over the study period, it is also advisable for future studies to further assess the influence of the vestibular depth upon the GW and GD changes. On the other hand, it should be noted that FEG performed simultaneous to anti-infectious therapy for peri-implantitis was associated to significantly more GD changes when compared to other interventions to augment KG/KM at the tooth and implant sites ($p=0.002$). This finding might have influenced the outcome. Hence, future studies should focus on the determinants of GD changes in FEGs used in standardized interventions at teeth and implant sites.

Conclusions

Free epithelialized grafts are exposed to dimensional changes that result in a reduction of approximately 40% of the original graft dimension - the decrease moreover being about 10% greater at implant compared to tooth sites. Baseline graft width and thickness, the type of intervention as well as the avascular area of the recipient site all influence the dynamic graft dimensional changes.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Figures and table legends

Figure 1. Illustrations depicting the intraoperative variables recorded at T0.

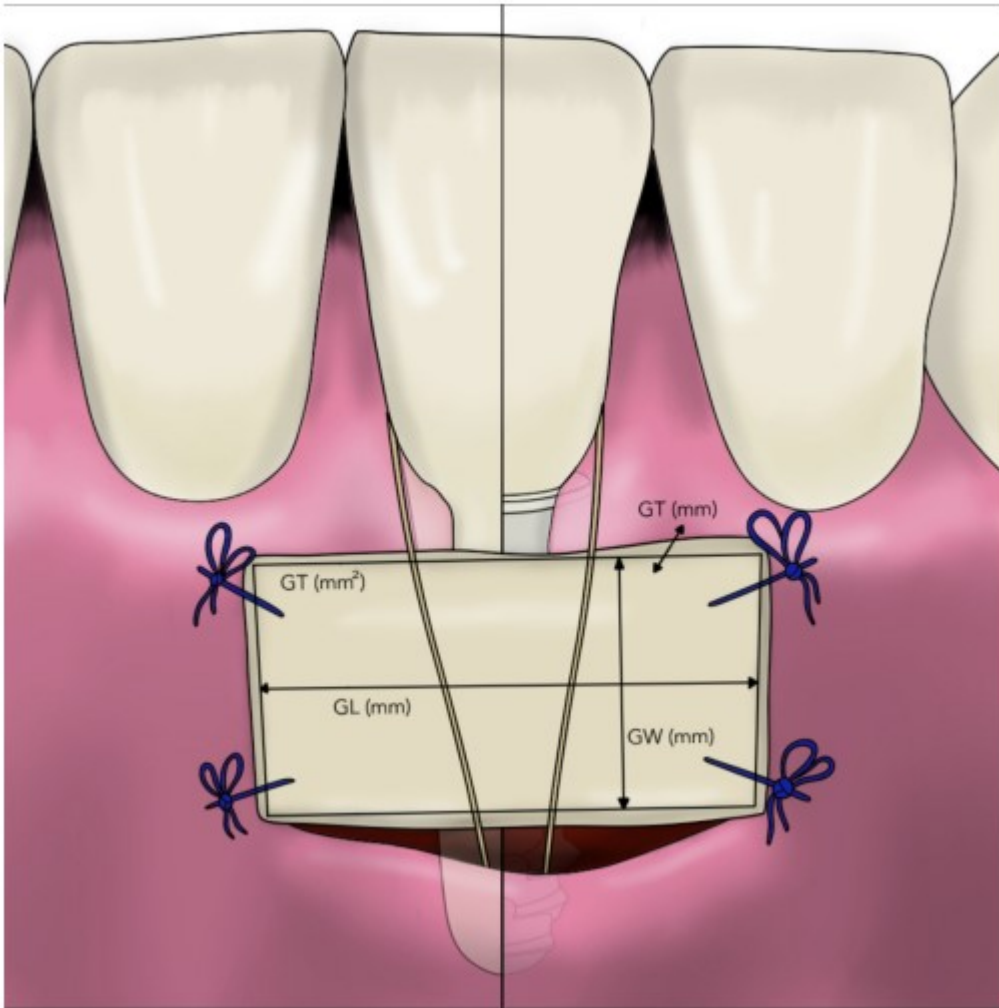


Figure 2. Percentage dimensional changes referred to total graft dimension (GD), total graft width (GW), and total graft length (GL).

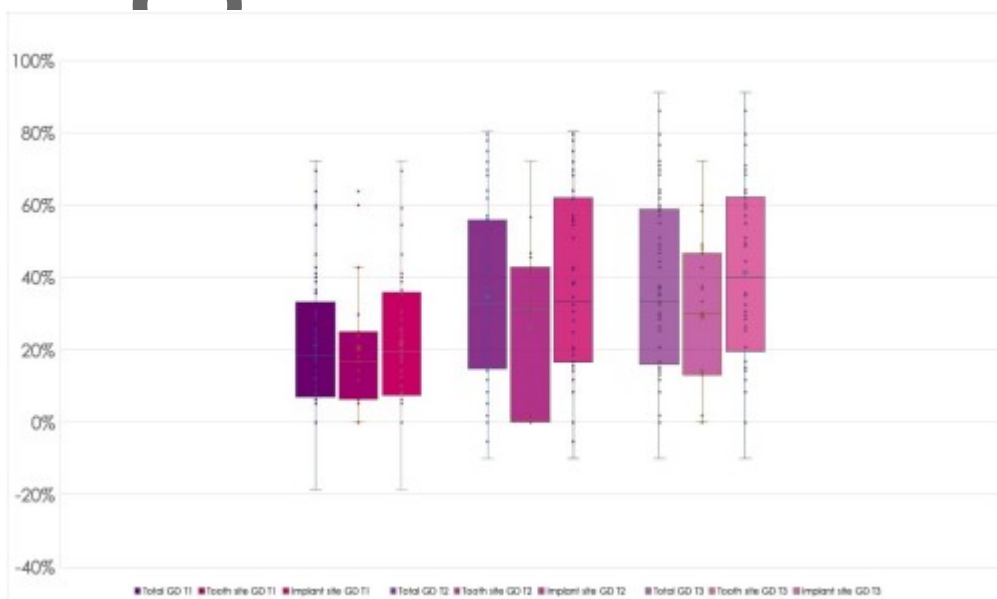


Figure 3. Epithelialized soft tissue graft for gaining keratinized tissue at tooth and implant sites.

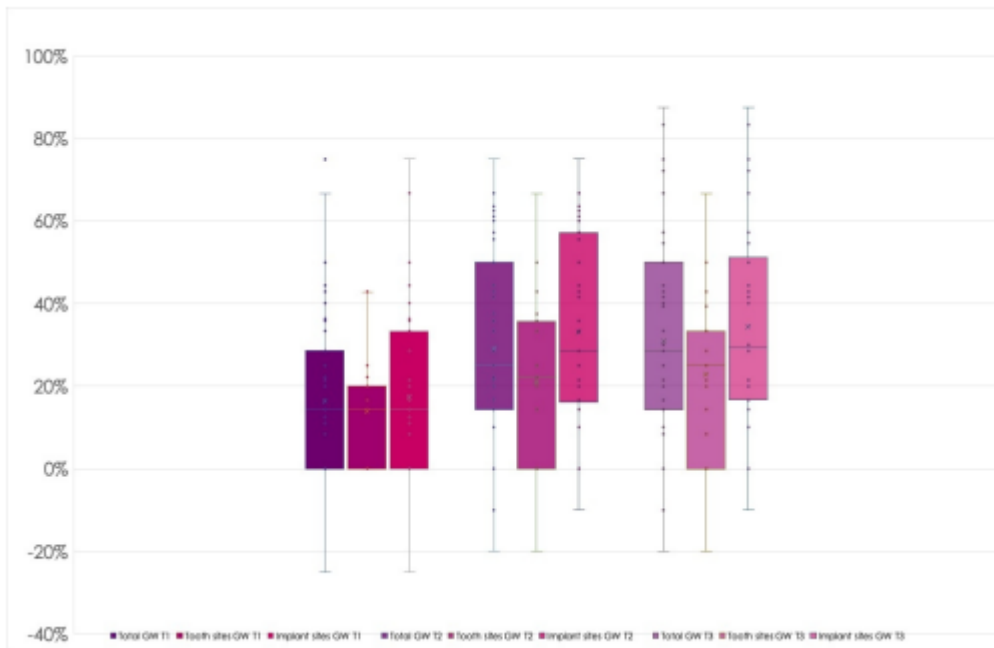


Table 1. Dimensional changes along the study period

	Linear changes Mean ± SD	% Change	p- value	Linear changes Mean ± SD	% Change	p- value	Linear changes Mean ± SD	% Change	p- value	Linear changes Mean ± SD	% Change	p- value
TOOTH SITES	T0 vs T1 (n=23)			T1 vs T2 (n=20)			T2 vs T3 (n=20)			Overall change (n=20)		
GW (mm)	0.96 ± 0.93	13.86%	<0.0005	0.85 ± 1.05	14.30%	0.004	0.14 ± 0.62	1.92%	0.315	1.84 ± 1.35	26.37%	<0.0005
GL (mm)	1.13 ± 2.26	7.52%	0.025	0.3 ± 1.69	0.15%	0.437	0.15 ± 1.31	1.30%	0.614	1.35 ± 1.09	9.75%	<0.0005
GD (mm ²)	21.09 ± 21.43	20.33%	<0.0005	13.33 ± 20.96	13.18%	0.010	1.9 ± 10	2.86%	0.406	33.88 ± 21.64	33.26%	<0.0005
IMPLANT SITES	T0 vs T1 (n=50)			T1 vs T2 (n=49)			T2 vs T3 (n=48)			Overall change (n=48)		
GW (mm)	1.26 ± 1.45	17.45%	<0.0005	1.08 ± 15.3	15.72%	<0.0005	0.15 ± 0.82	1.17%	0.253	2.54 ± 1.92	35.84%	<0.0005
GL (mm)	0.92 ± 0.90	5.33%	<0.0005	0.92 ± 2.22	5.03%	<0.0005	0.54 ± 1.11	3.19%	0.001	2.42 ± 2.70	13.12%	<0.0005
GD (mm ²)	27.11 ± 27.53	21.92%	<0.0005	20.42 ± 28.3	19.00%	<0.0005	4.64 ± 14.57	5.07%	0.032	53.43 ± 45.45	43.11%	<0.0005
TOTAL	T0 vs T1 (n=73)			T1 vs T2 (n=69)			T2 vs T3 (n=68)			Overall change (n=68)		
GW (mm)	1.16 ± 1.31	16.32%	<0.0005	1.01 ± 1.4	15.31%	<0.0005	0.15 ± 0.76	1.81%	0.137	2.33 ± 1.78	33.06%	<0.0005
GL (mm)	0.98 ± 1.45	6.02%	<0.0005	0.74 ± 2.08	3.61%	<0.0005	0.43 ± 1.18	2.64%	0.004	2.1 ± 2.38	12.13%	<0.0005
GD (mm ²)	25.21 ± 25.77	21.42%	<0.0005	18.36 ± 26.43	17.31%	<0.0005	3.83 ± 13.37	4.42%	0.061	47.67 ± 40.77	40.21%	<0.0005

GW: graft width; GL: graft length; GD: graft dimension

Table 2. Univariate and multivariate analysis of tooth group and implant group. Estimates of multilevel, random-intercept linear mixed models of percentage width change at 6 months compared to baseline. CI inf: inferior confidence interval 95%; CI sup: superior confidence interval 95%.

TOOTH SITE	Univariate analysis				Multivariate analysis			
	Coefficient	p-value	CI inf	CI sup	Coefficient	p-value	CI inf	CI sup
Patient level								
Age	0.002	0.749	-0.009	0.012				
Gender	0.027	0.816	-0.215	0.270				
Graft level								
Intervention								
Primary vs. Secondary	-0.055	0.795	-0.498	0.387				
Graft thickness	-0.219	0.033	-0.419	-0.020	-0.253	0.009	-0.435	-0.071
Recipient thickness	-0.055	0.593	-0.266	0.157				
Baseline length	-0.002	0.895	-0.032	0.028				
Single/Multiple sites	0.224	0.818	-0.180	0.225				
Ratio avascular/baseline graft dimension	0.885	0.943	-2.404	2.581				
Tooth level								
Avascular area	0.003	0.792	-0.020	0.027				
Baseline width	0.059	0.157	-0.025	0.143	0.076	0.037	0.005	0.147
IMPLANT SITE								
Patient level								
Age	0.009	0.008	0.002	0.015	0.006	0.028	0.001	0.012
Gender	0.099	0.378	-0.127	0.326				
Graft level								
Intervention								
Primary vs. all	-0.271	0.005	-0.453	-0.089				
Secondary vs. all	-0.025	0.838	-0.277	0.226				
Anti-infectious vs. all	0.207	0.014	0.045	0.368				
Graft thickness	-0.007	0.932	-0.167	0.153				

Recipient thickness	0.048	0.435	-0.075	0.170				
Baseline length	0.006	0.315	-0.006	0.018				
Mandible vs. Maxilla	0.029	0.722	-0.134	0.192				
Single/Multiple sites	0.066	0.339	-0.071	0.204				
Ratio avascular area/baseline graft area	3.20	0.105	-0.682	7.082				
Implant level								
Avascular area	0.038	0.016	0.007	0.069				
Anterior vs. Posterior	0.053	0.305	-0.050	0.156				
Baseline width	0.088	<0.0005	0.045	0.130	0.077	0.001	0.035	0.119

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