

# Clinical evaluations of free gingival grafting before implant placement to increase keratinized tissue width in molar regions: A retrospective case series

Ziyao Han<sup>1</sup>  | Yiping Wei<sup>1</sup>  | Cui Wang<sup>1</sup> | Gang Yang<sup>1</sup> | Wenjie Hu<sup>1</sup> | Kwok-Hung Chung<sup>2</sup>

<sup>1</sup>Department of Periodontology, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, Peking University School and Hospital of Stomatology, Beijing, China

<sup>2</sup>Department of Restorative Dentistry, University of Washington, Seattle, WA, USA

## Correspondence

Wenjie Hu, Department of Periodontology, Peking University School and Hospital of Stomatology, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, 22 Zhongguancun S Ave, Haidian District, Beijing 100081, China.  
Email: huwenjie@pkuss.bjmu.edu.cn

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## Abstract

**Objectives:** To evaluate the dimensional changes of the keratinized tissue width (KTW) in molar regions after augmentation by free gingival grafts (FGG) before implant placement.

**Material and Methods:** In seventeen patients, twenty implant sites in molar regions with KTW  $\leq 3$  mm at the buccal aspect received FGG 2 months before implant placement. KTW at the buccal aspect was measured before FGG (T0), immediately before implant placement (T1), at the time of impression taking for final prosthesis fabrication (T2), and at the end of the follow-up period after loading (T3, 12–48 months). Changes in KTW before and after FGG, as well as the alterations during the follow-up period after loading, were analyzed. Shapiro–Wilk test, paired Student's *t* test, and Wilcoxon signed-rank test were used for the data analysis at  $\alpha = 0.05$ .

**Results:** KTW at the buccal aspect of the alveolar ridge was observed with a significant gain of  $5.9 \pm 1.3$  mm at T1 ( $p < .001$ ). The shrinkage of KTW from T2 to T3 was 8.5%, which was limited but statistically significant ( $p = .008$ ). KTW at the buccal aspect of implant restorations was  $5.0 \pm 1.5$  mm at T3.

**Conclusions:** Within the limitations of the present study, our data suggest that using FGG to increase KTW in molar regions before implant placement had a predictable result. The buccal KTW had a limited reduction and was  $\geq 3$  mm with more than 12 months of follow-up after loading.

## KEYWORDS

dental implant, free gingival graft, keratinized tissue, screw-retained implant crown, soft tissue augmentation

## 1 | INTRODUCTION

The alterations of extraction sockets following tooth loss usually result in obviously absorbed alveolar ridges and are often

accompanied with soft tissue atrophy such as narrowing keratinized tissue (KT) and a shallow vestibule (Arnoux et al., 1998; Jiang & Lin, 2019). Controversial opinions exist in the topic of whether peri-implant keratinized tissue plays an important role in

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the maintenance of peri-implant tissue health and the long-term survival of dental implants (Bengazi et al., 1996; Bouri et al., 2008; Boynueğri et al., 2013; Chung et al., 2006; Crespi et al., 2010; Kim et al., 2009; Perussolo et al., 2018; Schrott et al., 2009; Warrer et al., 1995; Wennström et al., 1994; Wennström & Derks, 2012; Zigdon & Machtei, 2008). Abundant evidence has been found on the associations between lack of peri-implant KT and heavier plaque accumulation, which makes peri-implant tissues more vulnerable to inflammation (Bouri et al., 2008; Boynueğri et al., 2013; Buyukozdemir Askin et al., 2015; Chung et al., 2006; Crespi et al., 2010; Esfahanizadeh et al., 2016; Warrer et al., 1995; Zigdon & Machtei, 2008). This could be explained by the inadequate peri-implant KT resulting in impaired resistance to mechanical friction and weakened stability of the adherence between mucosal margin and the abutment surface, making it more difficult to achieve sufficient plaque control but easier for plaque accumulation (Adibrad et al., 2009; Grischke et al., 2019). In contrast, several studies have reported that peri-implant soft tissue health can be maintained even without KT (Bengazi et al., 1996; Kim et al., 2009; Wennström et al., 1994; Wennström & Derks, 2012). Some clinical studies described that patients complained about toothbrushing discomfort around implants with the width of KT (KTW) <2 mm (Perussolo et al., 2018; Souza et al., 2016). Moreover, Kim et al., (2009) discussed that increased risk of mucosal recession (MR) and marginal bone loss (MBL) may be associated with a narrow band of KT around dental implants. Similar results were also revealed in other studies (Bouri et al., 2008; Esfahanizadeh et al., 2016; Roos-Jansäker et al., 2006; Schrott et al., 2009; Zigdon & Machtei, 2008). The latest discussion of the peri-implant phenotype also proposed that <2 mm of peri-implant KTW was considered to be inadequate and was considered to be associated with the severity of peri-implant mucositis and future MBL (Avila-Ortiz et al., 2020; Grischke et al., 2019).

It is recommended that soft tissue augmentation procedures should be applied at implant sites with KTW <2 mm in order to maintain the peri-implant health, improve bleeding indices, and reduce MBL (Lin et al., 2018; Thoma, Alshihri et al., 2018). It is widely recognized that the application of free gingival graft (FGG) combined with apically repositioned flap (APF) can increase KTW around implants with high predictability (Bassetti et al., 2016; Fu et al., 2012; Park, 2006; Thoma, Buranawat, et al., 2014; Tavelli et al., 2020). The effects of FGG augmenting KTW around dental implants and the postoperative dimensional changes of KTW have been evaluated in several clinical studies (Baltacıoğlu et al., 2015; Basegmez et al., 2012; Elkhaweldi et al., 2015; Lee et al., 2010; Oh et al., 2020; Oh et al., 2017; Park et al., 2017; Schmitt et al., 2013; Schmitt et al., 2016; Tarasenko et al., 2020; Temmerman et al., 2018; Thoma, Naenni, et al., 2018). Heterogeneity of the study design and the outcome measures extensively existed between these studies, most of which chose to perform FGG during the second-stage surgery or after loading, and the follow-up period widely ranged from 6 weeks to 15 years after surgery.

Theoretically, soft tissue augmentation could be performed at any time before/during/after implant treatment (Lin et al., 2018). It was once commented that the therapeutic approach to increase KTW was indicated and was most predictable before insertion of the dental implant (Thoma, Mühlemann, et al., 2014). A recent systematic review confirmed that FGG can be used before implant placement to increase KTW and vestibular depth (Zucchelli et al., 2020). It can simplify the subsequent surgical procedures, since the soft tissue augmentation performed after loading is less predictable and usually performed as compensation for soft tissue deficiency, which would increase the difficulty of the surgery (Thoma, Buranawat, et al., 2014).

The outcomes of using FGG to increase KTW before implant placement are still sparse, and the augmentation of KT focusing in molar regions was infrequently evaluated among previous investigations. Therefore, the aims of the present retrospective case series were to evaluate (a) the effect of increasing KTW by using FGG in molar regions before implant placement and (b) the alterations of KTW at the buccal aspect of implants during the follow-up periods after loading. The null hypothesis was that KTW would be significantly increased by FGG performed before implant placement, decreased after implant reconstructions, and kept relatively stable after loading.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population, inclusion criteria, and exclusion criteria

In this study, the subjects was selected from partially edentulous patients who had received FGG in molar regions prior to implant placement in the Department of Periodontology, Peking University School and Hospital of Stomatology from October 2014 to March 2018. The present study was approved by the Institutional Review Board of Peking University School and Hospital of Stomatology (No. PKUSSIRB-201946083) in July 2019 and was in accordance with the Helsinki Declaration revised in 2013 and the STROBE guidelines. All the included patients had signed an informed consent. The inclusion and exclusion criteria were as follows:

#### 2.1.1 | Inclusion criteria

1. Patients who had undergone implant surgery in partially edentulous ridges in molar regions and had restored with implant-supported crowns after at least 12 months of loading;
2. FGG was performed at sites where KTW  $\leq$ 3 mm at the buccal aspect of the edentulous alveolar ridge with or without a shallow vestibule prior to implant placement;
3. In accordance with the definition of periodontal health described by Lang and Bartold (2018);
4. Patients with good compliance who attended to receive oral prophylaxis every 6 months after loading.

## 2.1.2 | Exclusion criteria

1. Smoking >10 cigarettes/day;
2. Systemic diseases that could affect wound healing;
3. History of bisphosphonate use or head and neck radiotherapy;
4. Incomplete medical records.

After preliminary screening, 21 individuals with 25 implant sites met the inclusion criteria. Three individuals with 4 implants were excluded due to heavy smoking, and 1 individual with 1 implant was excluded because some records of KTW after FG were missing. Seventeen individuals with 20 implants were eventually included in the present study.

## 2.2 | Treatment protocol

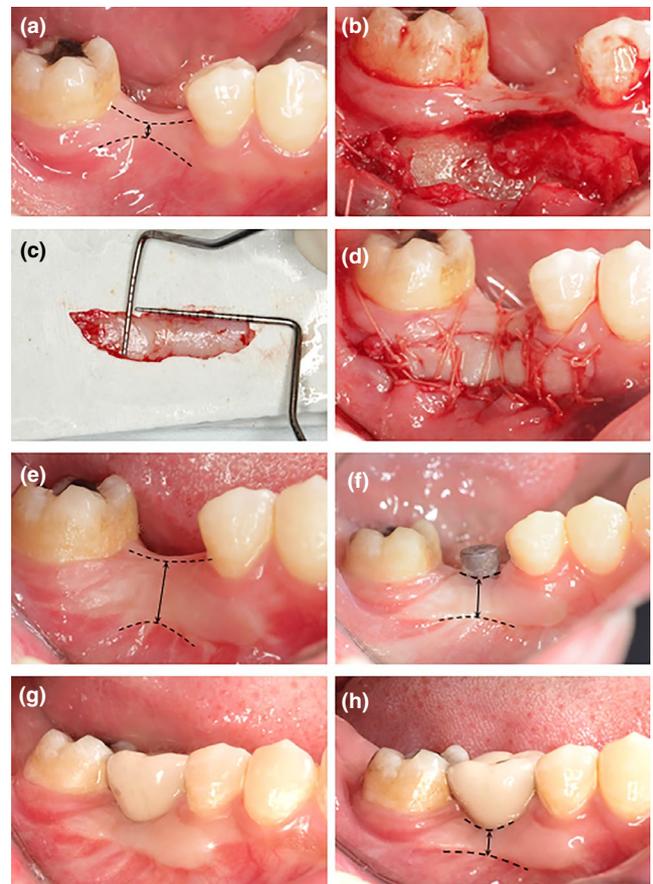
### 2.2.1 | Free gingival graft procedure

At partially edentulous posterior ridges in molar regions, FG was performed by the same experienced periodontist (WH) 2 months prior to implant placement. Under local anesthesia, the recipient bed was prepared with a horizontal incision made using a #15 scalpel blade at the mucogingival junction at the buccal aspect of the alveolar ridge, and vertical incisions were made at both ends of the horizontal incision and extended apically to the alveolar mucosa. The coronal and apical borders of the elevated flap were partial-thickness, while the periosteum was elevated at the middle part of the flap to completely cut off the muscle attachments. The flap was apically repositioned and fixed with the apical periosteum (5-0 Vicryl, Ethicon, Johnson & Johnson). A free gingival graft was harvested from the palate with a thickness of 1–1.5 mm. The length of the graft was chosen according to the size of the wound surface in the recipient area and the graft width was 6–8 mm. The graft was adapted and fixed apically to the original mucogingival junction at the recipient bed with interrupted sutures, and cross-mattress sutures were made from the apical periosteum to the coronal of the original mucogingival junction to keep the graft stable and fitted well (Figure 1). The palate was covered with a soft splint to protect the wound at donor site.

Patients were instructed to keep a soft-food diet postoperatively. Other instructions included tooth brushing avoiding the surgical area and mouth rinsing with 0.12% chlorhexidine twice daily for 2 weeks. Taking 250 mg of amoxicillin was advised 3 times per day for 1 week, 300 mg of Ibuprofen twice daily for 3 days, and then taken as needed. The splint could only be taken off during mealtimes and tooth brushing till the sutures were removed 2 weeks after surgery.

### 2.2.2 | Implant surgery procedure

Patients received a two-staged implant surgical approach by the same periodontist (WH) after 2 months of healing. A total of 20 Straumann bone-level implants ( $\varnothing$  4.1/4.8 × 8 mm, SLA coating;



**FIGURE 1** A typical case of increasing the buccal keratinized tissue width by using free gingival graft prior to implant placement. The mucogingival junction and the coronal reference point for measurements of the keratinized tissue width were marked with dotted lines in (a), (e), (f), and (h). (a) A narrow band of keratinized tissue at the buccal aspect of the edentulous ridge was recognized before free gingival graft (T0). (b) The prepared recipient bed during free gingival graft procedure. The elevated flap was sutured to the apical periosteum. (c) Free gingival graft harvested from the palate. (d) The free gingival graft was sutured to the recipient bed and fitted well. (e) Immediately before implant placement (T1, 2 months following free gingival graft), the buccal keratinized tissue width increased significantly. (f) Immediately before impression taking for final prosthesis fabrication (T2). (g) 2 years after loading. (h) An adequate band of keratinized tissue was maintained at the end of follow-up period after loading (T3)

Straumann, AG, Waldenburg, Switzerland) were inserted with submerged healing for 6 months before the second-stage surgery. Prosthetic reconstruction was initiated about 3 months after the second-stage surgery, and all the implant-supported restorations were screw-retained zirconia single crowns.

## 2.3 | Clinical measurements

All the clinical measurements were performed by a single calibrated examiner (WH). To assess the intra-examiner reliability, the KTW

at 20 randomly chosen molar sites was measured twice between 2 weeks. KTW at the buccal aspect was measured with a UNC-15 periodontal probe (Hu-Friedy) from the central of the (expected) implant position to the buccal mucogingival junction immediately before FGG, implant placement, and second-stage surgery, with an accuracy of 1 mm. Before the definitive prosthesis delivery (at the time of impression taking for final prosthesis fabrication) and at every 6 months after loading, KTW was measured from the mid-buccal mucosal margin of the abutment/crown to the mucogingival junction, which was determined by the difference of color and texture between KT and alveolar mucosa through pushing the alveolar mucosa coronally. During the follow-up period after loading, clinical parameters such as the plaque index (PLI), probing pocket depth (PPD), and bleeding index (BI) were also recorded, while only measurements of KTW at the end of follow-up period would be used for data analysis. The follow-up time ranged from 12 months to 48 months.

## 2.4 | Statistical analysis

In the present study, a single implant site was recognized as the test unit. The intraclass correlation coefficient and Cohen's kappa value used to assess the intra-examiner reliability of the KTW measurements were 0.958 (95% confidence interval [CI] = 0.840 to 0.989) and 0.910, respectively. In order to evaluate both the effect of using FGG in molar regions prior to implant placement to gain KTW and the shrinkage of FGG after loading, measurements of KTW at the following time points were extracted for the evaluation mentioned above: immediately before FGG (T0), before implant placement (T1), at the time of impression making for definitive prosthesis (T2), and the end of follow-up period after loading (T3). All the measurement data of KTW were entered into Excel 2016 (Microsoft Corporation) and analyzed by SPSS 20.0 (IBM Corporation). Descriptive statistical data included arithmetic mean, standard deviation (SD), median, and percentage. The differences of KTW (mm) between various measurement time points were analyzed by paired Student's *t* test or Wilcoxon signed-rank test after using the Shapiro–Wilk test to test the normality. The significance level was defined as  $\alpha = 0.05$ .

## 3 | RESULTS

### 3.1 | Data set

Seventeen patients (10 males and 7 females, age from 27 to 62 years old, mean age of 49.5 years old) were included in this study; each patient had 1 or 2 adjacent implant-supported crowns in molar regions. A total of 20 implant sites were included; 4 were in the maxilla and 16 in the mandible, with a mean KTW of  $1.3 \pm 1.3$  mm (range of 0–3 mm) at the buccal aspect of the alveolar ridge at T0 (Table 1). All the patients healed uneventfully following FGG and two-stage implant procedures, and the survival rate of

**TABLE 1** Demographics of patients & implant sites

Variable	
Age (years)	
Mean $\pm$ SD	49.5 $\pm$ 9.6
Median (range)	50 (27–62)
Gender (n [%])	
Male	10 (58.8)
Female	7 (41.2)
Implant location (n [%])	
Maxilla	4 (20)
Mandible	16 (80)
KTW at T0 (n [%])	
$\leq 1$ mm	11 (55)
$>1$ mm, $\leq 2$ mm	4 (20)
$>2$ mm, $\leq 3$ mm	5 (25)
Mean $\pm$ SD (mm)	1.3 $\pm$ 1.3
Median (range, mm)	1 (0–3)

Abbreviations: KTW, keratinized tissue width; n, sample number; SD, standard deviation; T0, immediately before the free gingival graft procedure.

implants during the follow-up period after loading was 100%. The follow-up time after loading ranged from 12 to 48 months (mean of 24.0 months). None of the implant sites showed the signs of peri-implant inflammations.

### 3.2 | Width of keratinized tissue

Table 2 presented the measurements of KTW at the buccal aspect of the edentulous ridge/implant at all the 20 sites, and the overall changes were illustrated in Figure 2. A statistically significant increase in KTW at the buccal aspect of alveolar ridge was detected at T1 (immediately before implant placement), from  $1.3 \pm 1.3$  mm to  $7.2 \pm 1.6$  mm ( $p < .001$ ). The gain of KTW was  $5.9 \pm 1.3$  mm (ranged from 4–8 mm). When the two-stage implant procedures were accomplished, the mean KTW measured at T2 was  $5.6 \pm 1.8$  mm. During the follow-up period after loading, the KTW at the mid-buccal aspect of the restoration showed a reduction of  $0.7 \pm 1.0$  mm, and the mean KTW at T3 was  $5.0 \pm 1.5$  mm. The shrinkage of KTW from T2 to T3 was about 8.5%, which was statistically significant ( $p = .008$ ).

## 4 | DISCUSSION

The main aim of this retrospective case series was to evaluate the result of KT augmentation by using FGG prior to implant placement in partially edentulous molar regions and the shrinkage of KTW after loading. The primary outcome was the measurements of KTW over the entire study period. The null hypothesis was accepted. Our results supported that (a) the application of FGG prior to implant

**TABLE 2** Measurements and the changes (mean  $\pm$  standard deviation) of the width of keratinized tissue (in mm) at the buccal aspect of the edentulous ridge/implant at various time points

Implant	Site	Follow-up time after loading (months)	Width of KT (mm)					
			T0	T1	$\Delta T1-T0$	T2	T3	$\Delta T2-T3$
1.	36	12	0	8	8	5	5	0
2.	36	12	0	7	7	3	4	-1
3.	37	12	0	7	7	4	4	0
4.	47	12	2	8	6	6	5	1
5.	47	12	3	7	4	6	5	1
6.	26	12	2	7	5	8	6	2
7.	37	12	3	8	5	7	6	1
8.	36	12	0	5	5	5	4	1
9.	37	12	0	5	5	3	4	-1
10.	46	12	0	6	6	4	3	1
11.	46	24	2	7	5	7	6	1
12.	16	30	2	8	6	6	6	0
13.	46	30	3	10	7	6	5	1
14.	16	36	0	7	7	7	7	0
15.	46	36	3	11	8	10	9	1
16.	36	36	0	7	7	5	5	0
17.	46	36	0	6	6	4	4	0
18.	47	42	1	5	4	3	3	0
19.	36	42	3	9	6	7	5	2
20.	36	48	1	5	4	6	3	3
Median (range)		18 (12-48)	1 (0-3)	7 (5-11)	6 (4-8)	6 (3-10)	5 (3-9)	1 (-1-3)
Mean (SD)		24.0 (13.2)	1.3 (1.3)	7.2 (1.6)	5.9 (1.3) <sup>a,**</sup>	5.6 (1.8)	5.0 (1.5)	0.7 (1.0) <sup>b,*</sup>

Abbreviations: KT, keratinized tissue; SD, standard deviation; Site, the site of implants, named with the FDI tooth numbering system; T0, immediately before the free gingival graft procedure; T1, immediately before implant placement; T2, immediately before the impression taking for final prosthesis fabrication; T3, the end of follow-up period after loading;  $\Delta T1-T0$ , differences of the width of keratinized tissue before and after free gingival graft;  $\Delta T2-T3$ , differences of the width of keratinized tissue before and after loading.

<sup>a</sup>Differences of the width of keratinized tissue before and after free gingival graft were analyzed using Wilcoxon signed-rank test.; <sup>b</sup>Differences of the width of keratinized tissue before and after loading were analyzed using paired Student's *t* test.; \*Statistically significant differences ( $p = .008$ ) for intragroup comparisons.; \*\*Statistically significant differences ( $p < .001$ ) for intragroup comparisons.

placement could significantly increase the KTW at the buccal aspect of the edentulous ridge in molar regions, and (b) KTW at the buccal aspect of the implant showed a limited shrinkage during the 12-48 months of follow-up after loading, indicating that the final gain of KTW by applying FGG prior to implant placement in molar regions was predictable.

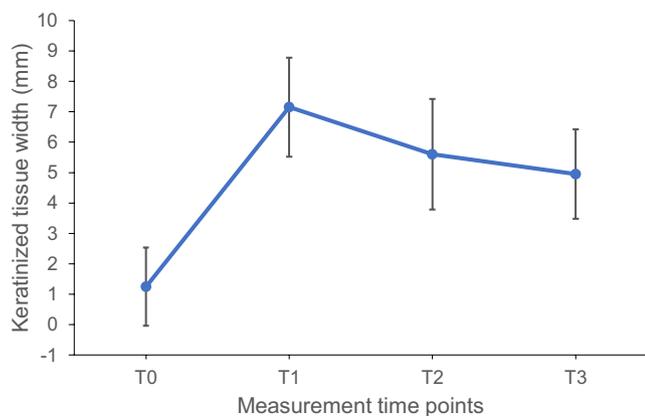
The progressive changes in KTW at the buccal aspect of all the 20 sites over the whole observation period are presented in Figure 3, which clearly showed that the KTW significantly increased after FGG, with a subsequent decrease from T1 to T2 at most sites. A band of KT with  $\geq 3$  mm (3-9 mm) width was successfully kept around all the 20 implants at the end of the 12-48 months of follow-ups, which was considered adequate, and the amount of KT was kept stable at most sites with  $>12$  months of follow-ups after loading. A significant increase ( $p < .001$ ) of KTW was recognized at T1 (2 months after FGG) in the present study, with a mean width of  $7.2 \pm 1.6$  mm

(ranging from 5 to 11 mm). The mean width gain of KTW at the buccal aspect of the alveolar ridge by using FGG was 5.9 mm, which was significantly higher than the results published in previous studies, ranging from 1.5 to 4.44 mm (Baltacıoğlu et al., 2015; Elkhaweldi et al., 2015; Lee et al., 2010; Oh et al., 2017; Park et al., 2017; Thoma, Naenni, et al., 2018). Greater amount of KTW augmentation ( $7.3 \pm 1.2$  mm) was reported in a split-mouth controlled clinical trial, while the measurement of KTW included both the buccal and lingual aspect of the alveolar ridge (Temmerman et al., 2018). Heterogeneity between the results could also come from the differences in surgical interventions and graft sizes.

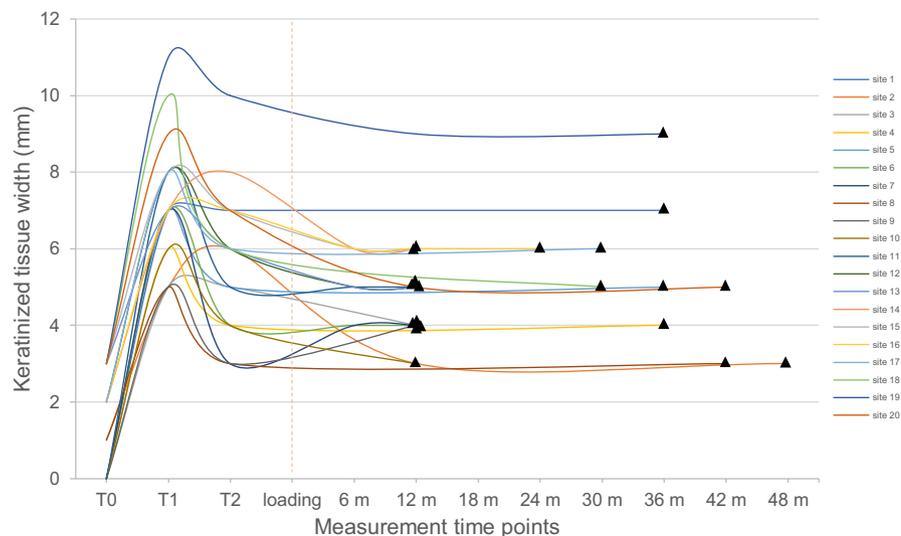
Oh et al., (2017) recommended that the augmentation of KTW would be restricted where the vestibular depth was too shallow. Moreover, prominent muscle attachments formed at the severely atrophic ridges or after bone augmentation should be released during the APF procedure, and the postoperative reattachment

which would impair the stability of the graft should be avoided as much as possible (Jiang & Lin, 2019; Schmitt et al., 2013). In order to prevent muscle reattachment at the augmentation area, Schmitt et al., (2013) used a vestibular retention splint to cover the recipient area after surgery and the splint was removed until the initiation of prosthetic reconstruction. On the contrary, Jiang and Lin (2019) demonstrated that the muscle reattachment could be prevented by complete removal of movable soft tissue on the flap and fixed on the apical periosteum without using the retention splint. In the present study, the elevated flap was designed as “partial-full-partial” thickness. The middle part of the elevated flap included the underlining periosteum, which allowed complete detachment of the muscular fibers.

The mean KTW presented with a reduction from T1 to T2 (from  $7.2 \pm 1.6$  to  $5.6 \pm 1.8$  mm), after two-stage implant procedures were completed. In the current study, the coronal reference point of KTW



**FIGURE 2** Changes of the width of keratinized tissue over various measurement time points (mean and standard deviation, mm). T0, immediately before the free gingival graft procedure; T1, immediately before implant placement; T2, immediately before the impression taking for final prosthesis fabrication; T3, the end of follow-up period after loading



**FIGURE 3** Changes of the width of keratinized tissue over the whole observation period of all the 20 sites. T0, immediately before the free gingival graft procedure; T1, immediately before implant placement; T2, immediately before the impression taking for final prosthesis fabrication; m, months

measurements was shifted to the mid-buccal mucosal margin of the abutment at T2, which was more apical than the previous reference points of T0 and T1 (central to the expected implant position). That might explain the decrease of KTW from T1 to T2. Another reason for the decrease in KTW might be the shrinkage during postoperative wound healing. It represented the exact changes of the keratinized tissue width at the buccal aspect of the implant site before and after implant reconstruction. In a prospective study assessing the clinical parameters around immediate submerged versus non-submerged implants, KTW around submerged implants had a  $1.86 \pm 1.29$  mm reduction from the time before tooth extraction to definitive loading (Cordaro et al., 2009). These could support the modification of the indications for FGG (KTW  $\leq 3$  mm rather than 2 mm) applied prior to implant placement.

The shrinkage of KT after loading in the present study was evaluated by comparing the KTW measured between the time of impression taking for final prosthesis fabrication and the end of follow-up period. Results showed that KTW had a limited but statistically significant reduction after loading ( $0.7 \pm 1.0$  mm/8.5%). That was comparable with a 15-year follow-up study, in which a 0.69 mm (approximately 16%) reduction of KTW was observed (Park et al., 2017). According to a controlled clinical study held by Schmitt et al., (2013), the minimal shrinkage of KTW was 14.59% at 30 days after FGG, while a 40.65% shrinkage was documented in a 5-year follow-up (Schmitt et al., 2016). Differences among the results may be due to the heterogeneity in graft materials and thickness, follow-up periods, and different indications for the augmentation of KT (Thoma, Buranawat, et al., 2014).

In this study, in spite of the different lengths of follow-up periods after loading, most implants with longer follow-ups ( $\geq 12$  months) did not present with more shrinkage of KTW at the buccal aspect, which indicated that the KTW would be relatively stable over time. Only 2 cases showed a slight increase of KTW (1 mm) after loading compared with that measured at T2. This is comparable with the results demonstrated in an extended follow-up study by Oh et al., (2020) that the KTW was well maintained from 18 months to 48 months

after FGG. According to the results of the present study, the selection of KTW measured at the time of impression taking for final prosthesis fabrication as the baseline to evaluate the shrinkage of KTW after loading was feasible.

The limitations of the present study were the lack of a non-grafted control group, a small sample size, and the retrospective design, which increased the risk of bias. The previous controlled clinical studies evaluating the application of FGG around implants demonstrated that a reduction of KTW was found in the non-grafted control group during the follow-up period, and the reduction was greater than in the test group which received FGG (Oh et al., 2017; Park et al., 2017).

## 5 | CONCLUSIONS

These results should be interpreted with caution, and further randomized controlled studies are needed to clarify the influence of possible confounders on KTW.

Within the limitations of this study, it does provide some valuable reference points to evaluate the long-term effect and stability of using FGG in molar regions before implant placement. The KT augmented by FGG showed limited shrinkage during the follow-up period after loading, and the KTW at the buccal aspect of all the implants was  $\geq 3$  mm throughout the end of the follow-ups, indicating that using FGG to increase KTW in molar regions before implant placement obtained predictable results and stability.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

## AUTHOR CONTRIBUTION

**Ziyao Han:** Data curation (equal); Formal analysis (lead); Methodology (equal); Validation (equal); Writing-original draft (lead); Writing-review & editing (equal). **Yiping Wei:** Data curation (supporting); Formal analysis (supporting); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Cui Wang:** Data curation (equal); Investigation (supporting); Writing-review & editing (equal). **Gang Yang:** Data curation (equal); Funding acquisition (supporting); Investigation (supporting); Validation (supporting); Writing-review & editing (supporting). **Wenjie Hu:** Conceptualization (lead); Data curation (lead); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Writing-original draft (supporting); Writing-review & editing (supporting). **Kwok-Hung**

**Chung:** Conceptualization (supporting); Formal analysis (supporting); Methodology (supporting); Supervision (supporting); Writing-original draft (supporting); Writing-review & editing (equal).

## DATA AVAILABILITY STATEMENT

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

## ORCID

Ziyao Han  <https://orcid.org/0000-0002-2023-0861>

Yiping Wei  <https://orcid.org/0000-0002-8517-3757>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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