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Impact of timing on soft tissue augmentation during implant treatment: A systematic review and meta-analysis

Running title: Impact of timing on soft tissue augmentation around implant

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ABSTRACT

Background: In order to achieve a predictable esthetic and functional outcome, soft tissue augmentation has become popular in implant treatment.

Objectives: The aim of this systematic review and meta-analysis was to assess the influence of different timing for soft tissue augmentation during implant treatment on soft tissue conditions and its stability.

Material and methods: Electronic and manual searches for articles written in English up to September 2017 were performed by two independent reviewers. Human clinical studies with the purpose of evaluating outcomes (at least 3 months follow-up) of autogenous soft tissue graft for augmentation during implant treatment, either simultaneous or after implant placement (staged), were included. Cumulative changes of keratinized tissue width (KTW), soft tissue thickness (STT) and mid-buccal mucosal recession (MR) data were analyzed with

a random effects model to compare the post-operative outcomes.

Results: Twenty-nine human studies (8 randomized clinical trials, 6 cohort studies and 15 case series) that met the inclusion criteria were included. For the overall data, the weighted mean STT gain (1 year after surgery) was 1.03 mm (95% CI: 0.78 to 1.29 mm), among which the simultaneous group was 1.12mm (95% CI: 0.75 to 1.49 mm) and staged group (3~ 6 months after implant placement) was 0.95 mm (95% CI: 0.58 to 1.31 mm). There was no statistically significant difference in KTW and MR between 3-month and more than 3 months after surgery.

Conclusions: This review revealed that the stability of soft tissue, in terms of keratinized tissue width and mid-buccal mucosal recession (MR), can be obtained 3 months after surgery. There is no difference between simultaneous and staged soft tissue augmentation during implant treatment and both procedures significantly enhance keratinized tissue width and soft tissue thickness.

Keywords: Dental implants; soft tissue augmentation; keratinized tissue; soft tissue thickness; mucosal recession; systematic review and meta-analysis

INTRODUCTION

Dental implants are now widely used for missing teeth replacement. Today, most implantologists have shifted their focus from obtaining osseointegration to achieving a pleasing aesthetic appearance. Hence, soft tissue augmentations around dental implants have slowly become an area of interest (Fu, Su, & Wang, 2012; Lin, Chan, & Wang, 2013; Thoma, et al., 2009; Thoma, Muhlemann, & Jung, 2014). When examining the soft tissue around the

implant, keratinized tissue (KT) width (KTW) and soft tissue thickness (STT) are the two most critical factors in esthetics, function and long-term implant stability. In other words, a lack of KT around implants has been associated with higher plaque accumulation, inflammation, more mucosa recession, and a less aesthetic appearance (Warrer, et al., 1995; Lin,et al.,2013). Furthermore, STT has been regarded as a key protective feature in preventing metal color exposure and minimizing mucosal recession (Jung, et al., 2008; Lops, et al., 2016). Hence, it is often suggested to augment thin tissue biotype, especially in the highly aesthetic areas (Rotundo, et al., 2015; Thoma, et al., 2009).

With respect to soft tissue augmentation surgery, different preferred materials and timings have been reported in various studies and reviews (Bassetti, et al., 2016; Esposito, et al., 2012; Fu, et al., 2012; Lin, et al., 2013; Rotundo, et al., 2015; Thoma, et al., 2009; Thoma, et al., 2014; Wu, et al., 2015). Over the years, autogenous soft tissue graft has been regarded as a gold standard for peri-implant soft tissue augmentation, although some have claimed that a new xenogenic collagen matrix might achieve comparable outcomes (Cairo, et al., 2017; Zeltner, et al., 2017). Aside from material of the graft, soft tissue augmentation surgeries can also be performed at different time-points during implant treatment. In one review, the various time points were used that included prior to implant placement, during the phase of tissue integration, or after final restoration. However, 4 to 6 weeks before abutment connection was regarded as an optimal time point for this procedure. On the contrary, soft tissue augmentation after final restoration could be less predictable because of highly-required skills (Thoma, et al., 2014). Currently, there is still no consensus in literature with regard to the effectiveness of timing upon soft tissue augmentation outcome. Furthermore, no study has compared a short- (<3month) versus long-term (≥3 months) STT

gain after soft tissue augmentation.

Therefore, the purpose of this systematic review and meta-analysis is to examine the effect of timing on soft tissue augmentation outcome (e.g., KTW, STT and MR) during implant treatment and to assess the soft tissue conditions as well as its stability overtime.

MATERIAL AND METHODS

This systematic review and meta-analysis was written and conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher, et al., 2009)

Focused question:

Based on Population, Intervention, Comparison, and Outcome (PICO) criteria (Stone, 2002), the question for the present literature search was addressed:

P: patients received dental implant placement in partial edentulous sites,

I: autogenous soft tissue graft (either free gingiva graft [FGG] or connective tissue graft [CTG]) was performed to improve the peri-implant soft tissue conditions,

C: perform soft tissue grafting at different time points during implant treatment, either simultaneously or after implant surgery (staged), and

O: improve the keratinized tissue width (KTW), soft tissue thickness (STT) and minimize mid-buccal mucosal recession (MR).

Therefore, the focused question for this review is “Does the timing of soft tissue grafting during implant therapy have an impact on the outcomes of peri-implant soft tissue conditions?”

Selection criteria

Eligible studies were included if they met the following criteria: 1. Any human studies (prospective or retrospective, randomized or not, cohort or case series trials); 2. Dental implants should be located in single or partial edentulous areas; 3. Soft tissue augmentation/ correction should be performed during or after implant placement; 4. At least 3 months follow-up period after soft tissue augmentation; 5. Autogenous soft tissue graft used for soft tissue augmentation/correction; 6. Data of KTW and/or STT and/or MR available; and 7. Full text in English.

Search strategy:

Electronic searches were performed in three databases—MEDLINE, EMBASE and Cochrane Central—for articles written in English up to 30 September 2017. The search terms comprised the combination of key words were:((Immediate implant [Title/Abstract]) OR (immediate implant placement [Title/Abstract]) OR (early implant [Title/Abstract])) AND ((soft tissue graft [Title/ Abstract]) OR (subepithelial connective tissue graft [Title/Abstract]) OR (connective tissue [Title/Abstract]) OR (FGG [Title/Abstract]) OR (gingival autograft [Title/Abstract]) OR (soft tissue augmentation [Title/Abstract]) OR (soft tissue transplantation [Title/Abstract]) OR (soft tissue defect [Title /Abstract]) OR (soft tissue correction [Title/Abstract])) AND ((reentry [Title/Abstract]) OR (re-entry [Title/Abstract]) OR (second stage[Title/Abstract]) OR (second- stage[Title/Abstract]) OR (stage two surgery[Title/Abstract])) AND ((attached gingiva[Title/Abstract]) OR (buccal soft tissue thickness[Title/Abstract]) OR (keratinized mucosa [Title/Abstract]) OR (soft tissue margin[Title/Abstract]) OR (attached mucosa [Title/Abstract]) OR (esthetic [Title/Abstract])).

In addition, a manual search of relevant articles was performed in the following journals: *Journal of Clinical periodontology, Journal of Periodontology, International Journal of Oral & Maxillofacial Implants, Journal of Oral and Maxillofacial Surgery, Clinical Oral Implants Research, Journal of Oral Rehabilitation, Clinical Implant Dentistry and Related Research, International Journal of Periodontics* and *International of Periodontics and Restorative Dentistry, Implant Dentistry, International Journal of Prosthodontics, International Journal of Oral and Maxillofacial Surgery, Journal of Oral Implantology* and *European Journal of Oral Implantology.*

The screening process was conducted by two independently reviewers (CL and ZC) (Figure1). According to selection criteria, titles and abstracts of search results were screened, and then potential articles were evaluated in full text. In the presence of duplicate publications, only the study with the most inclusive data was selected. The level of agreement between the reviewers regarding study inclusion was evaluated by κ value. If there was a disagreement, a decision determined by further discussion and consultation by another reviewer (HLW).

Risk of Bias Assessment

The quality assessment of included randomized controlled trials (RCTs) was conducted using the Cochrane collaboration's tool for assessing risk of bias. All selected RCTs were assessed by the RCT checklist, including random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selected reporting and other bias (Higgins, et al., 2011). If all criteria were met, degrees of bias were categorized as low risk. Those missing one criteria were considered as moderate risk, and those missing more than two criteria were ranked as high risk. At the same time, the included cohort study was

assessed by Newcastle-Ottawa scale, and each article was rated from 0 to 8 stars for each parameter in the scale (Department of Epidemiology and Community Medicine, 2013).

Data extraction and statistical analyses

The data from the eligible articles were extracted by two reviewers (CL and ZC) independently. Any inter-reviewer disagreement was resolved by discussion and consultation with another reviewer (HLW). Corresponding authors of studies were contacted in cases of unclear or missing data.

All statistical analyses were conducted using one statistical software program (Stata software, v14.0, StataCorp, College Station, TX.). For the overall studies, the cumulative mean changes of KTW and STT were calculated by the random effects model to avoid potential bias induced by methodological differences. Regarding the change of KTW, we conducted analyses based upon baseline KTW ($<$2mm or $\geq$ 2mm). The change of STT was calculated in simultaneous and staged group, respectively. Data of KTW and MR were analyzed with a random effects model to compare the post-operative 3-month outcome with that of more than 3 months. Heterogeneity was estimated by the Q statistic (significant at P <0.10) and quantified with the I^2 test. The value of I^2 $>$75% suggests high heterogeneity.(Higgins & Thompson, 2002)

The possibility of publication bias was assessed with Egger funnel plots for continuous data elements (supplementary Figure1). A significant publication bias was considered if P <0.05. However, results of these tests were not separately reported since this method is considered unreliable when studies included in the meta-analysis are <10.

RESULTS

Study selection

The screening process is shown in Figure 1. Using electronic and manual searching in PubMed and other database, 1855 and 351 potential related articles were selected respectively. After initial evaluation, 2169 studies that were assessed as reviews, animal studies or irrelevant articles were excluded. Thirty-nine articles had been through full text evaluation, and 10 of them were excluded with reasons (Table 1). At last, there were 20 studies included for further assessment in this systemic review. In addition, the k value for inter-reviewer agreement was 0.97 between the two reviewers.

Description of studies

Main features of the included studies were summarized with details in Table 2(a-e). To emphasize timing of soft tissue graft augmentation during implant treatment, all included articles were sorted into five groups:(1) Simultaneous soft tissue graft + immediate implant (SI group)(Table 2a); (2) Simultaneous soft tissue graft + non- immediate implant (SN group)(Table 2b); (3) Staged soft tissue graft + immediate implant (StI group)(Table 2c); (4) Staged soft tissue graft+ non-immediate implant (StN group)(Table 2d); (5) Staged soft tissue graft after final prosthesis loading (StP group)(Table 2e). Among all groups with staged soft tissue graft, soft tissue augmentation could be performed 1.5 to 6 months after implant placement, and the time points of intervention could also be found either prior, during stage 2 surgery or after implant restoration.

In SI group, 8 articles (Bianchi & Sanfilippo, 2004; Chung, et al., 2011; Covani et al., 2007; Kan, et al., 2009; Lee, et al., 2012; Migliorati, et al., 2015; Tsuda, et al., 2011; Zuiderveld, et al., 2017) were included. In general, CTG was mostly harvested from palate, however other

locations such as tuberosity or edentulous ridge were also considered in one article(Bianchi & Sanfilippo, 2004). In all articles except one, envelope flap without vertical releasing lines was performed and involved guided bone regeneration (GBR)(Lee, et al., 2012). Even though full mouth tooth sites were able to be chosen (Bianchi & Sanfilippo, 2004), the majority of implant sites were located at upper dentition, including aesthetic priority areas (maxillary premolar to premolar). On the other hand, only 2 studies(D'Elia, et al., 2017; Wiesner, et al., 2010) were associated with non-immediate implant and soft tissue graft at the same time in SNI group. Unlike tunnel technique for minimal-invasive considerations, one study placed soft tissue graft with concomitant GBR procedure, and access flap was performed(D'Elia, et al., 2017). In StI and StN groups, soft tissue augmentation can be performed from 1.5 to 6 months after implant placement or at the uncovered stage, and there was only one article included from the StI group(Cosyn, Bruyn, & Cleymaet, 2013). With respect to multiple implant sites, apically positioned flap (APF) combined with FGG were applied in 2 articles, and vestibuloplasty were also performed in extensive mandibular areas (Schmitt, et al., 2016; Schmitt, et al., 2013). In StP group, soft tissue augmentation was one of the treatment options after implant-supported prosthesis loading, and 4 articles(Lorenzo, et al., 2012; Roccuzzo, et al., 2014; Sanz, et al., 2009 ; Zucchelli, et al., 2013) were included. Only single implant situations could be dealt with soft tissue augmentation in all studies in this group, and 3 (Lorenzo, et al., 2012; Sanz, et al., 2009 ; Zucchelli, et al., 2013) of them used APF with CTG. Yet, Roccuzzo et al. harvested de-epithelized CTG from tuberosity as the graft material. Particularly, split-thickness envelope flap was used to repair peri-implant mucosal recession(Roccuzzo, et al., 2014).

Differences in measurement methods

As for measurement methods, different systems were used for soft tissue assessment (STT; Table 3). In the view of STT, most articles performed measurement with endodontic file with stopper, which would be fixed and transformed to numbers by periodontal probe or caliper (Wiesner, et al., 2010; D'Elia, et al., 2017; Zucchelli, et al., 2013). There was one exception where the study used an ultrasonic device (De Bruyckere, et al., 2015). In addition, the soft tissue change was measured by means of superimposed digital models, and the data obtained from linear deviation only represented the contour change rather than pure soft tissue gain (Zeltner, et al., 2017). In order to measure KTW, one study determined the location of MGJ by using the staining method (Zucchelli, et al., 2013) and the others performed the measurement by using a periodontal probe directly (Covani et al., 2007; Sanz, et al., 2009; Lee, et al., 2012; Lorenzo, et al., 2012; Schmitt, et al., 2013; Zucchelli, et al., 2013; Migliorati, et al.,2015; D'Elia, et al., 2017; Schmitt, et al., 2016). The measurement methods varied in MR assessment: 3 articles used casts with a customized stent (Chung, et al., 2011; Tsuda, et al., 2011; Cosyn, Bruyn, & Cleymaet, 2013); 3 studies utilized photographic images of surgical sites or casts (Lee, et al., 2012; Migliorati, et al.,2015; Zuiderveld, et al., 2017); 2 papers just measured with periodontal probes or calipers straight away (Lorenzo, et al., 2012; Roccuzzo, et al., 2014); and 2 studies followed the reference line of collateral or adjacent tooth to conduct the measurement (Bianchi & Sanfilippo, 2004; Zucchelli, et al., 2013).

Risk of Bias

Among all related articles, there were 8 RCTs, 1 controlled clinical trial, 4 cohort studies and 7 case series. The risk of bias in 8 included RCTs were assessed and summarized (supplementary Table1), 2 studies (Bianchi & Sanfilippo, 2004; Sanz, et al., 2009) (25%) of unclear risk of bias for allocation concealment, 1 study (Bianchi & Sanfilippo, 2004)(12.5%)

of high risk and 2 studies(Sanz, et al., 2009 ; Zuiderveld, et al., 2017) (25%) of unclear risk of bias for participants and personnel, and 1 study(D'Elia, et al., 2017) (12.5%) with selective reporting due to no baseline data. Also, most of the included articles (7/14, 87.5%) revealed an unclear risk of bias for blinding of the outcome assessment (Bianchi & Sanfilippo, 2004; Cairo, et al., 2017; D'Elia, et al., 2017; Lorenzo, et al., 2012; Sanz, et al., 2009 ; Zeltner, et al., 2017; Zuiderveld, et al., 2017). Only 1 controlled clinical trial had 7 stars and showed the "medium-high" level of evidence (Wiesner, et al., 2010) (supplementary Table 2). For the 7 case series(Chung, et al., 2011; Cosyn, et al., 2013; Covani, et al., 2007; De Bruyckere, et al., 2015; Lee, et al., 2012; Roccuzzo, et al., 2014; Tsuda, et al., 2011) and 4 cohort studies (Kan, et al., 2009; Schmitt, et al., 2016; Schmitt, et al., 2013; Zucchelli, et al., 2013), the majority (7/11, 63.6%) were prospective in design with consecutively enrolled subjects. Six (6/11, 54.5 %) articles were assessed as low-moderate risk. Among the 5 high-risked articles, all of them were due to the lack of data for KTW, STT. Hence, the evaluation of primary outcomes of soft tissue condition are mainly based on the articles with low-moderate risk.

Results for KTW

With respect to KTW at peri-implant area, 4 RCTs (Cairo, et al., 2017; D'Elia, et al., 2017; Migliorati, et al., 2015; Sanz, et al., 2009), 1 cohort (Zucchelli, et al., 2013) and 2 case series (Covani, et al., 2007; Lee, et al., 2012; Sanz, et al., 2009) were included. Based on the baseline data of KTW, these studies could be divided into two groups: ≥2mm (Cairo, et al., 2017; D'Elia, et al., 2017; Migliorati, et al., 2015) and < 2mm(Covani, et al., 2007; Lee, et al., 2012; Sanz, et al., 2009 ; Zucchelli, et al., 2013). From baseline to more than 1 year, the weighted mean of KTW change was 0.55 mm (95% CI: -0.34 to 1.45 mm) in ≥ 2mm group, and 2.56 mm (95% CI: 2.30 to 2.82 mm) in < 2mm group with 1.69mm (95% CI: 0.87 to

2.52 mm) as the overall mean value (Figure 2(a)). Adding timing as one of the considerations, all relevant articles were distributed into 4 groups based on baseline and different time-points of soft tissue augmentation. KTW revealed more change in the group with KTW<2mm but similar values in simultaneous and staged groups (2.61 mm (95% CI: 2.32 to 2.97 mm); 2.38 mm (95% CI: 1.85 to 2.970 mm))(Figure 2(b)). There were 5 publications (Lee, et al., 2012; Migliorati, et al., 2015; Sanz, et al., 2009 ; Schmitt, et al., 2016; Zucchelli, et al., 2013) with complete data, and their values of KTW were compared at 3 months and > 3 months healing. The results revealed that the KTW gain at 3-month was more than that at > 3-month (weighted mean difference [WMD]: 0.21, 95% CI: 0.13 to 0.55) with a low degree of heterogeneity (I^2 =0.0%; p=0.81); however, no statistically significant difference was found (Figure 3).

Results for STT

To focus on the effects of timing on soft tissue augmentation in STT, 7 articles were extracted with 4 (D'Elia, et al., 2017; Migliorati, et al., 2015; Rungcharassaeng, et al., 2012; Wiesner, et al., 2010) in simultaneous and 3 (Cairo, et al., 2017; De Bruyckere, et al., 2015; Schmitt, et al., 2016) in staged treatment groups. To specify the time points, soft tissue augmentation could be performed 3 to 6 months after implant placement (De Bruyckere, et al., 2015; Schmitt, et al., 2016)) or even at stage 2 surgery (Cairo, et al., 2017). The weighted mean STT gain (1 year after surgery) was 1.03 mm (95% CI: 0.78 to 1.29 mm), among which the simultaneous group was 1.12mm (95% CI: 0.75 to 1.49 mm) and staged group was 0.95 mm (95% CI: 0.58 to 1.31 mm) (Figure 4).

Results for MR

With regards to mid-buccal MR change after soft tissue graft, 6 articles were qualified

(Chung, et al., 2011; Cosyn, et al., 2013; Lee, et al., 2012; Lorenzo, et al., 2012; Migliorati, et al., 2015; Tsuda, et al., 2011). Results showed no statistically significant difference in MR between 3 months after soft tissue augmentation and 1- year followed-up (-0.13; 95% CI: -0.34 to 0.09; I^2 = 0.0%; P = 0.961)(Figure 5).

DISCUSSION

Undoubtedly, more emphasis has been placed on soft tissue surrounding peri-implant areas for improving aesthetic outcomes and minimizing future biological complications (Esposito, et al., 2012; Fu, et al., 2012; Lin, et al., 2013; Rotundo, et al., 2015; Thoma, et al., 2009; Wu, et al., 2015). Previous implant soft tissue studies have mostly aimed to examine biological width, papilla height, keratinized tissue and tissue biotype (Thoma, et al., 2009; Thoma, et al., 2014). However, our review was focused on the KTW and STT to illustrate their influence on the peri-implant soft tissue stability and its relationship to the mid-buccal MR. Furthermore, we have also assessed the impact of soft tissue grafting timing during implant therapy.

Width of keratinized tissue gain

Conflicting data existed if KT is needed for prevention of peri-implantitis as well as maintenance of implant long-term stability. However, majority of the studies are in favor of having a band of KT to not only improve aesthetic appearance, but also to facilitate oral hygiene performance for better implant long-term stability (Bouri, et al., 2008; Chung, et al., 2006; Kim, et al., 2009; Lin, et al., 2013; Thoma, et al., 2014). Among all related articles, APF plus vestibuloplasty and autogenous grafts such as FGG or SCTG, was regarded as the most effective technique to obtain KT (Bassetti, et al., 2016; Thoma, et al., 2009; Thoma, et al., 2014). One review showed that APF, APF with SCTG and roll techniques performed at

second stage surgery were able to gain 4.63 mm, 4.10 mm and 1.35 mm of KTW, respectively (Bassetti, et al., 2016). In spite of less surgical time and patients' comfort in alternatives (Thoma, et al., 2014), autograft (FGG, SCTG) remains the gold standard for soft tissue augmentation in terms of KTW, tissue thickness, aesthetic and long-term volume stability (Fu, et al., 2012; Park, 2006). Hence, the present review focused on the autogenous soft tissue graft related studies.

Surprisingly, different baseline values of KTW can end up with different change 1 year later. For example, the weighted mean KTW change was 0.55 mm in ≥2mm group and 2.56 mm in < 2mm group. The result of this review implied the predictability of soft tissue augmentation in sites with baseline KTW < 2 mm. On the contrary, the necessity of additional soft tissue graft might not be needed in sites of ≥2mm due to limited KTW augmentation.

Soft tissue thickness

Soft tissue volume comprises two parts in different directions: biological width (BW) and soft tissue thickness (STT)(Thoma, et al., 2014). According to previous studies, BW has been known as the vertical part of soft tissue around implants, which also permits a safe zone for the bone underneath (Abrahamsson, Berglundh, & Lindhe, 1997; Berglundh & Lindhe, 1996; Berglundh, et al., 1991). On the other hand, STT is the horizontal part of soft tissue often known as biotype. Interestingly, one theory suggested that adequate STT around implant could prevent the crestal bone loss (Linkevicius, et al., 2015); however, the 2mm threshold of thickness was measured at the crestal portion of flap. In other words, STT in that article was more likely to reference biotype instead of biological width. It is because of the different views of STT in various articles that precautions must be taken when interpreting this result.

Different methods/tools were used for soft tissue assessment, which include but are not

limited to sounding with stopper, ultrasonic device, cast-superimposed technique and three-dimension image based on intraoral photos (Zelner, et al., 2017). To minimize the possible bias, the meta-analysis of STT merely included the data from sounding (Wiesner, et al., 2010; D'Elia, et al., 2017; Zucchelli, et al., 2013) and ultrasonic measurement (De Bruyckere, et al., 2015). To be more specific, the details in STT change for ultrasonic device could be up to 0.01mm, which is more accurate than the conventional tools (endodontic ruler, caliper or periodontal probe). Additionally, the location of MGJ can only be found by both a functional test and the staining method, so the determination of KT border might have some impacts on measurement errors. Aside from STT and KTW, the various measurement methods and different reference lines in MR should be mentioned in related articles. Hence, these different assessment tools might explain some of the discrepancies noted among studies, and the data extracted from different articles should be interpreted with cautions as well.

To facilitate evaluation the effect of timing on soft tissue augmentation outcomes, we sub-divided the assessment into 2 groups (simultaneous or staged). Data from this review showed 0.95 mm and 1.12 mm of STT gain in staged and simultaneous groups, respectively. However, no significant difference was found. Soft tissue graft during implant treatment could definitely be considered to improve the contour and esthetics, especially in thin biotype. Interestingly, the soft tissue stability on simultaneous soft tissue graft remains a concern among many clinicians (Bassetti, et al., 2016; Thoma, et al., 2014), although, both groups achieved comparable STT gain. Additionally, Thoma et al. regarded soft tissue augmentation after final restoration as a procedure with less predictability and is often used as a rescue approach. Yet, 4 articles included in staged approach group showed favorable outcomes, which might attribute to limited defect size (single implant) (Lorenzo, et al., 2012; Roccuzzo,

et al., 2014; Sanz, et al., 2009 ; Zucchelli, et al., 2013). In summary, soft tissue augmentation during implant therapy can be applied in different timing with predictability.

Results from this review showed soft tissue graft prevent mid-facial MR during implant therapy. Furthermore, there is no statistically significant difference in MR between 3 months after soft tissue augmentation and 1-year follow-up. This is in agreement with one review that showed flapless, bone graft in bone gap and SCTG placement were able to prevent mid-facial MR (Lin, et al., 2013). The flapless approach often leads to less recession when compared to flapped ones (Raes, et al., 2011). The bone graft in the gap can provide the foundation support for soft tissue in-growth and autogenous soft tissue graft results in coronal movement of mucosal level, that is, all to minimize MR. Nevertheless, autograft placement can increase KTW but at the cost of 0.5 mm recession of flapping opening (Esposito, et al., 2012). In present review, the overall mean value from baseline was 0.13 mm with the range from -0.34 mm~0.09 mm, which was in line with the values in the previous studies.

The favorable outcome noted in our article may be largely due to autogenous soft tissue grafts being the only ones assessed. This is in agreement with the systematic review paper that discussed soft tissue graft with implant therapy. In this paper, authors only extracted data from articles with least 6 months follow- up. They found shrinkage of soft tissue ranged from 0.34~ 6.8 mm with the highest reduction observed at first month to 3~6 months (Bassetti, et al., 2016).

Data from this paper showed techniques used for harvesting autogenous soft tissue did not affect the outcomes**.** This can be explained by the minimal-invasive (envelope, pouch, tunnel) harvesting technique employed in most of these papers. On the contrary, APF with graft were preferred in articles with multiple implants and soft tissue augmentation after final restoration

in single implant, because these approaches can significantly increase the amount of STT and KTW.

The limitations of this review should be acknowledged. 1) Most of the included studies had small sample sizes and short follow-up periods; 2) There were inconsistencies in methodologies with various treatment modalities; 3) The present review includes only English language publications, which may have introduced selection bias. Therefore, there is a need for a better RCT with longer follow-up, larger sample size and clearer study design that compares simultaneous and staged soft tissue augmentation.

CONCLUSION

This review revealed that the stability of soft tissue, in terms of keratinized tissue width and mid-buccal mucosal recession (MR), can be obtained 3 months after surgery. There is no difference between simultaneous and staged soft tissue augmentation during implant treatment and both procedures significantly enhance keratinized tissue width and soft tissue thickness.

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Figure Legends

Figure 1. The articles selection process.

Figure 2(a). Meta-analysis was conducted in assessing keratinized tissue width (KTW) change of different thickness (≥2mm versus <2mm) at different time points

Figure 2(b). Meta-analysis of keratinized tissue width (KTW) was performed to look into the influence of timing on soft tissue augmentation during implant therapy

Figure 3. Meta-analysis was performed to examine keratinized tissue width (KTW) change at 3 month and 3 months later after surgery.

Figure 4. Meta-analysis was conducted to examine soft tissue thickness (STT) change at different time points.

Figure 5. Meta-analysis of mucosal recession (MR) changes at 3 month and 3 months later after surgery.

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Table 1 Excluded articles with reasons.

Author (Year)	**Excluded articles with reasons**
Kablan, et al. (2014)	Soft tissue they used is “free fat tissue” from buccal fat pad. No data of soft tissue conditions.
Dee, et al. (2016)	Insufficient sample size. No data of soft tissue conditions.

Stimmelmayr, et al. (2010, 2011)	No data of soft tissue conditions.
Grunder (2011)	
Rungcharassaeng et al. (2012)	
Rosa, et al. (2014)	
Koleman, et al. (2016)	
Hanser, et al. (2016)	
Bienz et al. (2017)	
Redemagni, et al. (2009)	Incomplete data of soft tissue conditions.
Schneider et al. (2011)	
Tunkel et al. (2013)	
Sanz-Mart et al. (2016)	Soft tissue placement in pontic sites without implants.
Herford et al. (2011)	No free soft tissue graft was performed. (They used connective tissue flap instead.)
Chaar et al. (2017)	No free soft tissue graft was performed. (They used modified palatal pedicle connective tissue flap instead.)
Park et al. (2012)	No free soft tissue graft was performed.(The article focused on modified roll technique.)
Raghoebar et al. (2009)	Soft tissue augmentation before implant placement or simultaneous during ridge
Karaca et al. (2015)	preservation procedure.

Table 2 Included articles divided in different groups with general information and clinical outcomes in keratinized tissue width (KTW), soft tissue thickness (STT) and mid-buccal mucosal recession (MR)(mm). 2(a) Simultaneous soft tissue graft + immediate implant (SI group); 2(b) simultaneous soft tissue graft + non-immediate implant (SN group); 2(c) staged soft tissue graft + immediate implant (StI group); 2(d) staged soft tissue graft + non-immediate implant (StN group); 2(e) staged soft tissue graft after final prosthesis loading+ non-immediate implant (StP group).

Simultaneous soft tissue graft + immediate implant

Table 2(a) SI group

Authors (Order)	Study type	SCTG donor site	Number (test/ control)	Technique	Recipient Location	KTW (Mean (SD))			STT (Mean (SD))			MR (Mean (SD))	
						Baseline	3m	>3m	Baseline	3m	>3m	3m	>3m
Bianchi et al (2004)	RCT	P,T, E	116/ 20	Envelope	Full mouth	NR	2 (No SD)	NR	NR	NR	NR	1(No SD)	1(No SD)
Covani et al. (2007)	CRS	P	10	No flap	Upper Pr-Pr	1.3(0.6)	NR	4.1(0.5)	NR	NR	NR	NR	NR
Kan et al (2009)	CRS	P	20	Bilaminar envelope	Upper C-C	NR	NR	NR	NR	NR	NR	NR	0.13(0.61)
Chung et al. (2011)	CRS	P	10	Envelope	C-C+Pr	NR	NR	NR	NR	NR	NR	3.89(1.1)	3.72(1.03)
Tsuda et al. (2011)	CRS	P	10/28	Envelope	Upper Pr-Pr	NR	NR	NR	NR	NR	NR	2.3(1)	2.25(1.21)
Lee et al (2012)	CRS	P	11	Flapped	Upper L-L	1.1(0.4)	3.7(0.7)	3.6(0.5)	NR	NR	NR	2.1(0.7)	1.7(0.7)
Migliorati et al (2015)	RCT	P	24/23	No flap	Upper Pr-Pr	3.3(1.2)	3.1(1.2)	3(1.2)	1.1(0.6)	2.3(0.8)	1.8(0.8)	0.42(0.5)	0.73(0.51)
Zuiderveld et al (2017)	RCT	T	29/29	Envelope	Upper Pr-Pr	NR	NR	NR	NR	NR	NR	0.1(0.9)	0(0.3)

RCT, randomized clinical trial; CCT, controlled clinical trial; CRS, case report/series; SCTG, subepithelial connective tissue graft; FGG: free gingival graft; P: palate; T: tuberosity; E: edentulous; Pr: premolar ; C: canine; L: lateral; NR, not reported;

SD, significant difference; F/U: follow- up.

Simultaneous soft tissue graft + Non-immediate implant													
Authors	**Study type**	**SCTG donor site**	**Number (test/ control)**	**Technique**	**Location**	KTW (Mean (SD))			STT (Mean (SD))			MR (Mean (SD))	
						Baseline	3m	1-2Y	Baseline	3-6m	1Y	3m	>3m
Weisner et al. (2010)	CCT	P	10/10	Open flap	Posterior mandible	NR	NR	NR	2 (0.47)	NR	3.2(0.42)	NR	NR
D'Elia et al. (2017)	RCT	P	16/16	Access flap	Upper Pr-Pr	4.06(0.8)	5.4(1.05)	5.16 (1.22)	2.7 (1.4)	3.56 (1.23)	3.7(1.0)	0	0.23(0.34)

Staged soft tissue graft + Immediate implant													
Authors	**Study type**	**Donor site**	**Numbers (test/ control)**	**Technique**	**Location**	KTW (Mean (SD))			STT (Mean (SD))			MR (Mean (SD))	
						Baseline	3m	1-2Y	Baseline	3-6m	1Y	3m	>3m
Cosyn et al.	CRS	P	22→21→20	Envelope	Upper Pr-Pr	NR	NR	NR	NR	NR	NR	0.3(0.8)	0.2(0.4)

(2013)				(pouch)									

Table 2(b) SN group

Table 2(c) StI group

Table 2(d) StN group

Staged soft tissue graft + Non-immediate implant													
Authors	**Study type**	**Donor site**	**Numbers (test/ control)**	**Technique**	**Location**	KTW (Mean (SD))			STT (Mean (SD))			MR (Mean (SD))	
						Baseline	3m	6m-1Y	Baseline	1-3 m	6m-1Y	3m	>3m
Schmitt et al. (2013)	CRS	P (FGG)	7/7	APF+ vest	Mandible (Multiple)	0.88(0.65)	9.81(2.45)	3.7(No SD)	NR	NR	NR	NR	NR
De Bruykee et al. (2015)	CRS	P	37	Envelope	Upper Pr-Pr	NR	NR	NR	1.51(0.46)	2.6(0.54)	2.5(0.56)	NR	NR
Schmitt et al. (2016)	CRS	P (FGG)	21	APF+ vest	Mandible (Multiple)	0.7(0.69)	9.39(2.66)	8.46(2.68)	NR	NR	NR	NR	NR
Zelner et al.(2017)	RCT	P	10	Pouch	Upper Pr-Pr	NR	NR	NR	NR	NR	0.54(0.71)	NR	NR

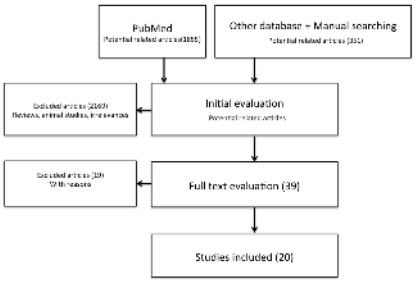
Table 2(e) StP group

Staged soft tissue graft (After final prosthesis loading) + Non-immediate implant													
Authors	**Study type**	**Donor site**	**Numbers (test/ control)**	**Technique**	**Location**	KTW (Mean (SD))			STT (Mean (SD))			MR (Mean (SD))	
						Baseline	3m	6m-1Y	Baseline	3-6m	1m	3m	>3m
Sanz et al. (2009)	RCT	Palate	12	APF	Full mouth	0.42(0.51)	2.67(1.44)	2.75(1.5)	NR	NR	NR	NR	NR
Lorenzo et al. (2012)	RCT	Palate	12	APF	Mandible	1.75	NR	2	NR	NR	NR	1.17(1.3)	1.17(1.27)
Zuccheli et al. (2013)	CRS	Palate	10	APF	Maxilla	0.2(0.42)	3.1(0.87)	2.6(0.96)	0.92(0.27)	NR	2.5(0.39)	NR	0.1(0.44)
Roccuzzo et al. (2014)	Case reports	De-epithelialized tuberosity	6	Envelope (split thickness)	Maxilla (Single)	NR	NR	NR	NR	NR	NR	NR	0.3(0.3)

Table 3. Differences of measurement methods in included articles

Authors	Measurement (STT)	Measurement (KTW)	Measurement (MR)
Bianchi et al (2004)	NR	NR	Refer to emergence line
Covani et al. (2007)	NR	Periodontal probe directly	NR
Kan et al (2009)	NR	NR	NR
Chung et al. (2011)	NR	NR	Casts+ customized stent+ probe
Tsuda et al. (2011)	NR	NR	Casts+ customized stent
Lee et al (2012)	NR	Periodontal probe directly	Digital photographic images
Migliorati et al (2015)	Stent+ endodontic reamer with stopper	Periodontal probe directly	Casts were photographed with millimeter grid
Zuiderveld et al (2017)	NR	NR	Photographs+ periodontal probe
Weisner et al. (2010)	Endodontic micro-opener+ silicone stop (1mm below crest)+ endodontic longimeter	NR	NR
D'Elia et al. (2017)	Calibrated endodontic file (2mm below crest) + Periodontal probe	Periodontal probe directly	Periodontal probe directly

Cosyn et al. (2013)	NR	NR	Customized stent+ probe
Schmitt et al. (2013)	NR	Periodontal probe directly	NR
De Bruykere et al. (2015)	Ultrasonic device (EPOCH, Olympus, Aartselaar, Belgium)	NR	NR
Schmitt et al. (2016)	NR	Periodontal probe directly	NR
Zelner et al.(2017)	Digital models to obtain linear change (Not included in meta-analysis)	NR	NR
Sanz et al. (2009)	NR	North Carolina University probe	NR
Lorenzo et al. (2012)	NR	North Carolina University probe	North Carolina University probe directly
Zuccheli et al. (2013)	Aneesthesia needle+ silicone stop (1.5 mm below crest)+ caliper	Lugol staining + probe	Comparing to contralateral tooth
Roccuzzo et al. (2014)	NR	NR	Castroviejo Caliper Short (Salvin Dental Specialties, Inc., USA)



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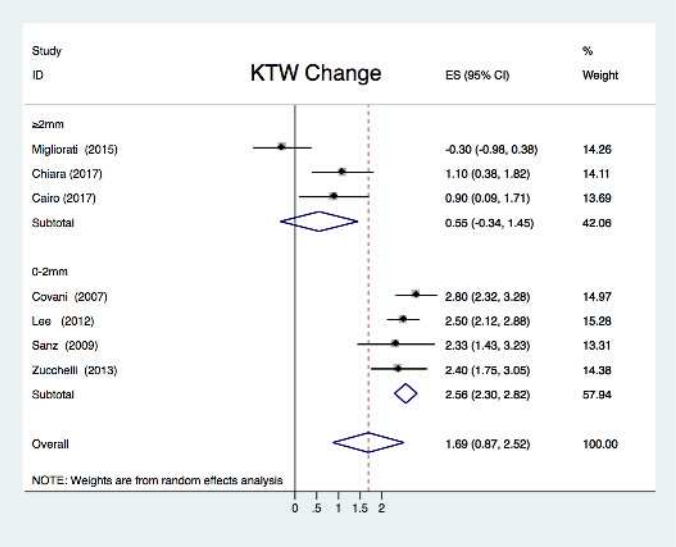

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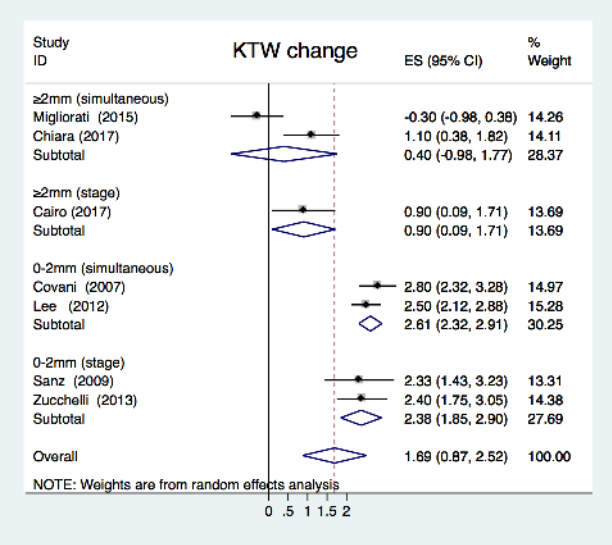

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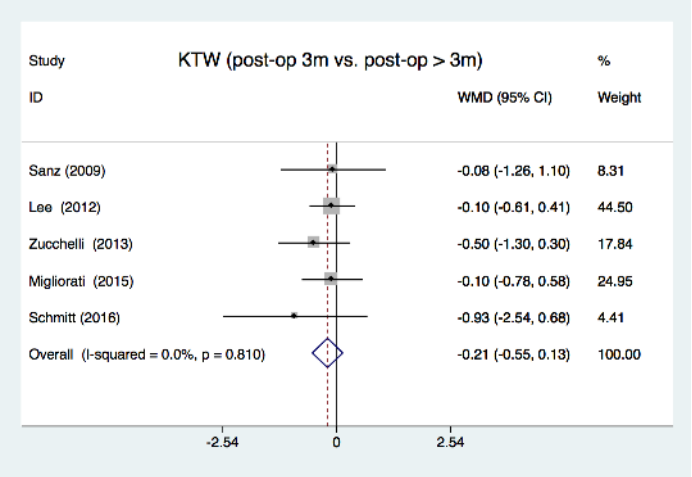

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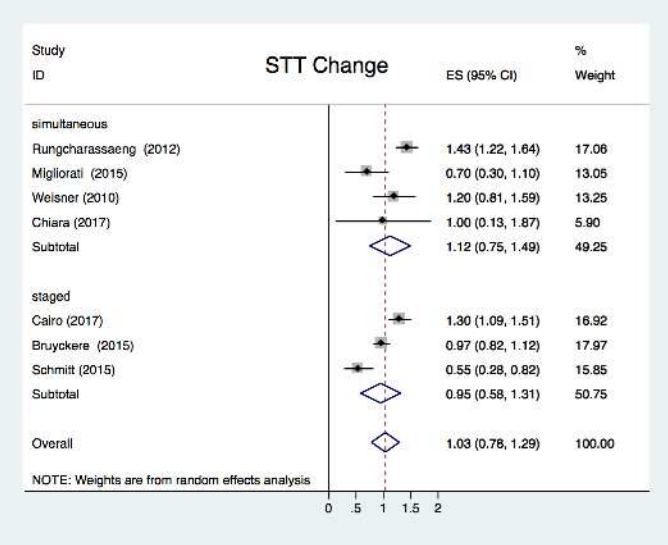

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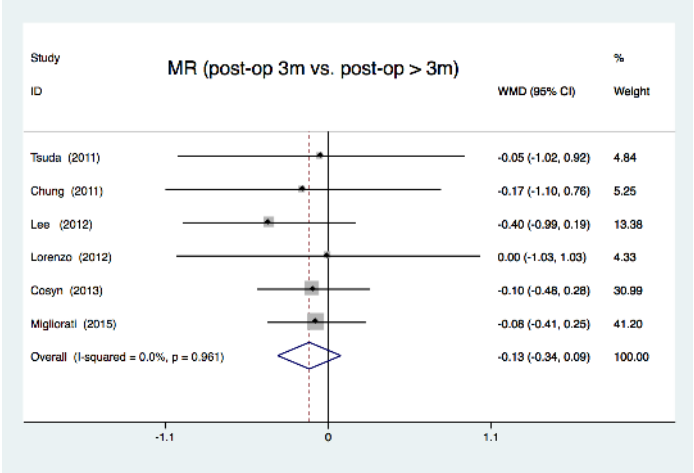

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