

Efficacy of Xenogeneic Collagen Matrix to Augment Peri-implant Soft Tissue Thickness Compared with Autogenous Connective Tissue Graft: A Systematic Review and Meta-Analysis

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Purpose: Several approaches for increasing peri-implant mucosal thickness have been proposed, including autogenous, allogeneic, and xenogeneic grafts. The objective of this meta-analysis was to analyze whether xenogeneic matrices are viable alternatives to autogenous soft tissue grafts in peri-implant soft tissue augmentation. **Materials and Methods:** A systematic search was performed to select randomized clinical trials that compared connective tissue grafts and xenogeneic collagen matrices. The primary outcomes were the mucosal thickness and keratinized mucosa changes, while the secondary outcomes were patient morbidity, painkiller consumption, and surgical time required for the procedure. **Results:** Seven randomized clinical trials were included for the final evaluation with a total number of 218 implant sites (108 in the connective tissue graft group, 110 in the collagen matrix group) with 3 to 12 months (mean: 6 months) follow-up period. Results showed mucosal thickness increase in both buccal and crestal sites, but it did not yield statistical significance. The keratinized mucosa gain difference was only -0.06 mm (95% CI [-30.0, 0.18]) between the treatments. The postsurgical discomfort, increased consumption of painkillers, and reduction of treatment time (15.46 minutes less) differed significantly in favor of the collagen matrix group. **Conclusion:** Within the limits of this study, it can be concluded that collagen matrix and connective tissue graft are equivalent in peri-implant soft tissue augmentation. *INT J ORAL MAXILLOFAC IMPLANTS* 2019;34:1059–1069. doi: 10.11607/jomi.7497

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The recent consensus report from the Osteology Foundation concluded that an adequate peri-implant mucosal thickness and keratinized mucosa width can provide greater Plaque Index and Gingival Index reduction as well as a higher marginal bone stability compared with sites lacking (or with minimal) mucosal thickness and keratinized mucosa.¹ The correlation

between a thin mucosa and greater marginal bone loss has been documented.^{2,3} Linkevicius et al showed that regardless of the implant-abutment interface location, the thickness of the mucosa was a critical factor for marginal bone stability.² In addition, a mucosal thickness of at least 2 mm is considered the threshold for having better esthetic outcomes.⁴ Several materials have been proposed to increase the peri-implant mucosal thickness; these include but are not limited to connective tissue grafts,⁵ allogeneic and xenogeneic grafts,^{6,7} and platelet-rich fibrin.⁸ Among all, the most effective materials seem to be those involving autogenous connective tissue graft.⁹ Utilization of connective tissue graft to enhance peri-implant soft tissue thickness has been revealed to prevent mucosal recession, inflammation, and peri-marginal bone loss.^{10–12}

Peri-implant mucosa differs greatly from periodontal soft tissue. Indeed, the longer junctional epithelium, parallel orientation of the connective tissue fibers, lower number of fibroblasts, and reduced vascularity are characteristics of peri-implant soft tissue.^{13,14} As a result

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of parallel orientation of the connective tissue fibers, the soft tissue seal around the dental implant may be weaker than the natural teeth.¹⁵ Thus, it is believed that disease spreads much faster in implants than in natural teeth, which is why the literature advocates to have an acceptable width of keratinized mucosa to hinder marginal bone loss and maintain peri-implant health.^{16,17} It has been suggested that a free gingival graft harvested from the palate is the most effective technique in recreating keratinized mucosa at implant sites.^{1,9} Nevertheless, a significant increase in keratinized peri-implant mucosa width has also been described using connective tissue graft.^{5,18}

Connective tissue graft and free gingival grafts have been extensively investigated to manage gingival recessions and for increasing keratinized tissue around teeth and have shown high success rates.^{19–22} However, several complications related to palatal harvesting have been reported, including increased postoperative pain, prolonged bleeding, donor site infection, and palatal sensory dysfunction.^{23–25} Therefore, it is not surprising that studies assessing patient-reported outcomes have shown a greater preference toward soft tissue graft substitutes.^{26,27} In addition, recent studies have suggested that the xenogeneic collagen matrix may provide comparable outcomes to the connective tissue graft in root coverage procedures and at peri-implant sites.^{5,7,28–30} Accordingly, the goal of this review was to determine if xenogeneic collagen matrices are viable alternatives to connective tissue graft in peri-implant soft tissue augmentation.

MATERIALS AND METHODS

Study Registration and Protocol Development

Prior to the execution of the study, this review proposal was registered in the PROSPERO International Prospective Register of Systematic Reviews, with the identification number CRD42018091207.

The systematic review was conducted by abiding to the Preferred Reporting Items Systematic review and Meta-Analyses (PRISMA) statement and checklist,³¹ and the patient, intervention, comparison, outcomes (PICO) method (Fig 1).

Patient, Intervention, Comparison, Outcome (PICO) Question

In patients requiring soft tissue augmentation in association with dental implant therapy (P), would patients benefit more from a xenogeneic collagen matrix (I) in comparison to a connective tissue graft (C) when considering mucosal thickness, width of keratinized mucosa, patient's morbidity, painkiller consumption, and surgical time (O)?

Focused Questions

Is xenogeneic collagen matrix comparable to the autogenous connective tissue graft in augmenting keratinized mucosa width and mucosal thickness at implant sites?

Information Sources and Screening Process

Two independent reviewers (S.B. and L.T.) conducted the electronic and manual literature searches, covering studies until February 2018 across the National Library of Medicine (MEDLINE by PubMed), EMBASE, and the Cochrane Oral Health Group Trials Register. Furthermore, a manual hand-search of journals related to the field (from January 2013 to February 2018) was also performed, including an entire search of *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Clinical Oral Implants Research*, *International Journal of Oral & Maxillofacial Implants*, *Clinical Oral Investigations*, *International Journal of Periodontics & Restorative Dentistry*, and *Clinical Implant Dentistry and Related Research*. Ultimately, previous systematic reviews investigating implant and root coverage procedures for soft tissue improvements were also screened for article identification. Moreover, some of the authors were contacted to inquire for further information regarding their investigations.

Eligibility Criteria

Studies were selected for inclusion if they met the following criteria: (1) human randomized clinical trials; (2) surgical treatment aimed at increasing peri-implant soft tissue thickness; (3) comparison of connective tissue grafts (control) versus xenogeneic collagen matrices (test); (4) a follow-up of at least 3 months; and (5) reported outcome measures keratinized mucosa gain or mucosal thickness gain following the surgical intervention. The exclusion criteria consisted of: (1) study with < 10 patients; (2) in vitro and preclinical studies, cohort studies, case-control studies, case series, case reports, and systematic reviews; (3) surgical treatment including materials other than an autogenous connective tissue or collagen matrix xenograft; (4) soft tissue augmentation performed before implant placement; and (5) soft tissue augmentation performed but not in direct contact with a dental implant. Moreover, studies dealing with soft tissue treatments to increase keratinized mucosa or mucosal thickness around implants were not considered.

Data Extraction

Subsequent to duplicate removal, the remaining articles were checked and excluded by relevance with screening the titles and reviewing the abstracts by two investigators (S.B., L.T.). Finally, full-text reading by an additional reviewer (J.G.) was performed, according

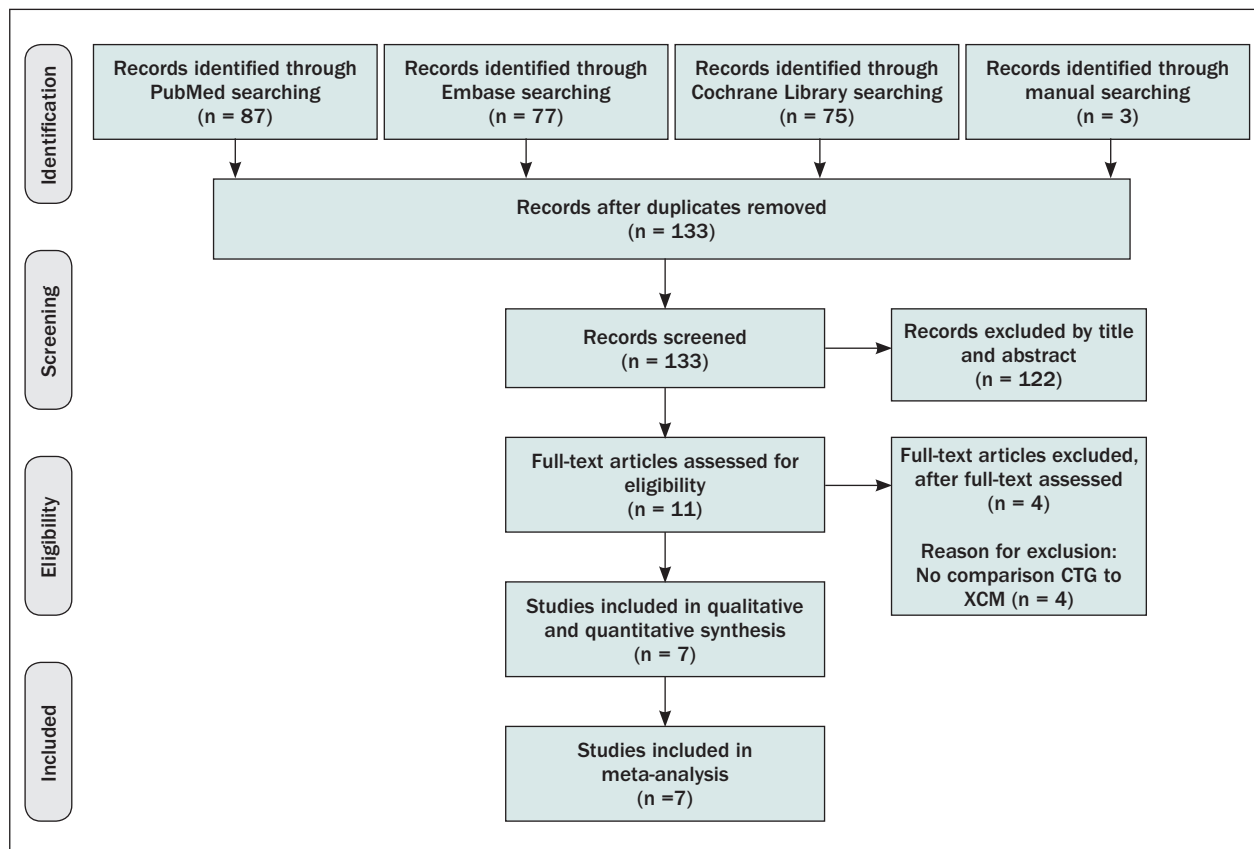


Fig 1 PRISMA flowchart.

to the predetermined criteria for confirming the eligibility of each study as previously mentioned in the inclusion and exclusion criteria. The primary outcomes were the mucosal thickness and keratinized mucosa changes, while the secondary outcomes were patient morbidity (as assessed with postoperative pain), painkiller consumption, and surgical time.

Patient characteristics, treatments, and clinical outcomes data were systematically and independently extracted by two investigators (J.G., S.B.). When important clinical data were not present, the authors of the investigations were contacted for pursuit of the missing data. At each stage, disagreement between reviewers was resolved through discussion and consensus. In case a disagreement persisted, a third reviewer (L.T.) was decisive and led to an agreement.

Statistical Analysis

All analyses were performed by an author with expertise in statistical analyses (S.B.) using the metafor package³² in Rstudio (Rstudio Version 1.1.383, RStudio). Changes in the primary (mucosal thickness, keratinized mucosa) and secondary (postoperative morbidity, painkiller consumption, chair time) outcome measures were considered for comparison between the connective tissue graft and collagen matrix groups. For

all the outcome measures, inverse variance weighted means and weighted mean differences were obtained with 95% confidence intervals (CI). Afterward, each study contribution was assessed accordingly, and the random effects model was selected (the DerSimonian-Laird method), as heterogeneity and certain methodologic differences were presumed among trials. Forest plots were produced to summarize the difference in the outcomes between the connective tissue graft and collagen matrix groups, and a threshold of .05 was set for statistical significance. Heterogeneity among studies was assessed with chi-square (χ^2) test and the I^2 statistics test according to the Cochrane Handbook for systematic reviews.³³ Additionally, funnel plots were used to demonstrate potential publication bias among the selected randomized clinical trials. Lastly, to evaluate the level of agreement between the two independent researchers, Cohen's Kappa index was used for assessment.

RESULTS

Study Selection

The search process based on the PRISMA guidelines is detailed in Fig 1. After full-text screening, four articles

Table 1 General Overview of the Included Studies

Study	Study design, follow-up times	Age (mean) (SD) (y), patients, and implants (n)	Systemic, periodontal status, and smoking habits	Time of grafting in relation to implant therapy	Location	Site, setting, and funding
Sanz et al ⁴¹ (2009)	RCT 1, 3, 6 months	59.2 (CTG); 64.3 (CM) Patients n = 20 Implants n = 14	Systemic and periodontal healthy, good plaque control (FMPS < 20%) smokers < 10 cig/day	After crown placement	Max-mand Ant-post	Spain, Public Hospital, partially supported by company
Lorenzo et al ³⁹ (2011)	RCT 1, 3, 6 months	63 (7.9) (CTG); 62 (8.7) (CM) Patients n = 24 Implants = 24	Systemic and periodontal healthy, good plaque control (FMPS < 20%) smokers < 10 cig/day	After crown placement	Max-mand Ant-post	Spain, Public Hospital, supported by company
Thoma et al ⁷ (2016)	RCT 1, 3 months	42.7 (19.1) (CTG); 43.8 (13.2) (CM) Patients n = 20 Implants n = 20	Systemic and periodontal healthy, BPE < 2 smokers < 10 cig/day	After implant placement (implant placed 6 weeks to 6 months before)	Max PM to PM	Switzerland, University, partially supported by company
Zeltner et al ⁴² (2017)	RCT 1, 3 months	42.7 (19.1) (CTG); 43.8 (13.2) (CM) Patient n = 20 Implants n = 20	Systemic and periodontal healthy smokers < 10 cig/day	After implant placement (implant placed 6 weeks to 6 months before)	Max-mand PM to PM	Switzerland, University, partially supported by company
Cairo et al ⁵ (2017)	RCT 1, 3, 6 months	48.3 (11.8) (CTG); 50.3 (12.4) (CM) Patients n = 60 Implants n = 60	Systemic and periodontal healthy, probing depths ≤ 5 mm, FMPS and FMBS ≤ 15% smokers < 10 cig/day	During second surgery implant uncovering	Max-mand	Italy, self and company supported
Puzio et al ⁴⁰ (2017)	RCT 3, 12 months	41.1 (11.9) (CTG); 42.1 (15.3) (CM) Patients n = 57 Implants n = 75	Systemic and periodontal healthy (plaque score API 20%, FMBS 10%) smokers < 10 cig/day	During second surgery implant uncovering	Max-mand PM to PM	Poland, University and company supported
Huber et al ³⁸ (2018)	RCT 1 year	43.4 (18.8) (CTG); 44.1 (12.8) (CM) Patients = 20 Implants = 20	Systemic and periodontal healthy, BPE < 2 smokers < 10 cig/day	During second surgery implant uncovering	Max PM to PM	Switzerland, University, partially supported by company

FMPS = full mouth plaque score; FMBS = full mouth bleeding score; BPE = basis periodontal examination; NR = not reported.

were excluded,^{34–37} and therefore, seven randomized clinical trials, treating a total number of 218 implant sites (108 in the connective tissue graft and 110 in the collagen matrix group) were included in the present review.^{5,7,38–42} The inter-reviewer reliability in the screening and inclusion process, as assessed with Cohen's Kappa, corresponded to 0.87, and 0.93 for the assessment of titles and abstract, and full-text evaluation, respectively.

Study Characteristics

All the seven randomized clinical trials selected for the analysis included two parallel arms, one treatment arm including the use of connective tissue graft, and in the other arms, all patients were treated with collagen

matrix.^{5,7,38–42} All studies reported that participants were periodontally healthy without smoking more than 10 cigarettes/day. Soft tissue grafts were performed in two after implant placement^{39,41} and the remaining five were before crown placement.^{5,7,38,40,42} The follow-up time in all studies ranged from 3 to 12 months (mean: 6 months) (Table 1).

Quality Assessment

The result of bias risk assessment for the included randomized clinical trials, using The Cochrane Risk of Bias Tool, is summarized in Appendix Table 1 (see online version of this article at quintpub.com). Six trials were considered as having a low risk of bias,^{5,38–42} while only one trial⁷ was observed to have a moderate risk of bias.

Table 2 General Characteristics of the Intervention and Results

Study (year)	Preoperative preparation	Treatment control group	Treatment test group	Postsurgical treatment/Postop instructions	Suture removal	Painkiller consumption	Postop discomfort	Authors' conclusion
Sanz et al ⁴¹ (2009)	OHI, prophylaxis, new toothbrush 4 weeks before	CTG	XCM	NSAID (ibuprofen 400 mg), CHX for 2 weeks OHI, POH	10 days	CM less than CTG STD	VAS 0–10 CM less pain in 10 and 30 days STD	XCM increased the width of KG or GT as effectively and predictably as the CTG, but it was associated with a significantly lower patient morbidity.
Lorenzo et al ³⁹ (2011)	OHI, prophylaxis, new toothbrush 4 weeks before	CTG	XCM	NSAID (ibuprofen 400 mg), CHX for 2 weeks OHI, POH before	10 days	Less painkillers in CM group but no STD	VAS 0–10 Less reported in CM group but no STD	Mean gain KT similar in both groups and less pain, less pain medication, and less surgery time with XCM but no STD
Thoma et al ⁷ (2016)	500 mg mefenamic acid, 1.5 mg amoxicillin, CHX 60"	CTG	XCM	NSAID (mefenamic 500 mg) 3 days, amoxicillin 7 days, CHX for 2 weeks POH before	7–10 days	Less analgesics in CM without STD	VAS 0–10 and OHIP-G14 A trend for VCMX to be associated with less morbidity but without STD	No STD, XCM and CTG in periodontal parameters and increase KT and GT
Zeltner et al ⁴² (2017)	500 mg mefenamic acid, 1.5 mg amoxicillin, CHX 60"	CTG	XCM	NSAID (mefenamic 500 mg) 3 days, amoxicillin 7 days, CHX for 2 weeks POH before	7–10 days	XCM less painkillers STD	XCM less postoperative pain STD	Differences between the two groups were not significant.
Cairo et al ⁵ (2017)	NR	CTG	XCM	NSAID (ibuprofen 600 mg) + CHX 2/day POH before 3- and 6-month follow-up	7 days	XCM less painkillers STD	VAS 0–100 XCM significantly lower intensity of postsurgical	Similar KT and GT, but XCM is associated with shorter surgical time, lower postoperative morbidity, less anti-inflammatory tablets consumption, and higher patient satisfaction.
Puzio et al ⁴⁰ (2017)	OHI, prophylaxis, 10 days before surgery. 2 g amoxicillin or 600 mg clindamycin 1 hour before, CHX 1 minute	CTG	XCM	Augmentin twice/day, CHX 2 weeks, ibuprofen 400 mg or paracetamol 1 g 3 times a day, 3 days	14 days	NR	NR	Both CTG and XCM increase KT, but higher values of KT were noted using CTG augmentation.
Huber et al ³⁸ (2018)	500 mg mefenamic acid, 1.5 mg amoxicillin, CHX 60"	CTG	XCM	NSAID (mefenamic 500 mg), 3 days, amoxicillin 7 days, CHX for 2 weeks POH before	7–10 days	NR	NR	No significant changes over time nor STD between the groups.

CTG = connective tissue graft; XCM = xenogeneic collagen matrix; KT = keratinized tissue; GT = gingival thickness; NR = not reported; OHI = oral hygiene instruction; POH = professional oral hygiene; NSAID = nonsteroidal anti-inflammatory drugs; STD = statistical differences.

Meta-Analysis

Data from the selected randomized clinical trials were extracted and organized (Table 2). Among the seven selected randomized clinical trials, five trials reported on the outcome of mucosal thickness increase on the buccal site,^{5,7,38,40,42} and two studies also evaluated the mucosal thickness increase on the crestal (occlusal) site.^{7,42} The changes in the keratinized mucosa (apico-coronal) were evaluated in four trials^{5,38,39,41}

collectively, and further subdivided into the bilaminar^{5,38} and the apically positioned flap-based surgical technique.^{39,41} The comparison of postoperative discomfort was assessed in four trials,^{5,7,39,41} postoperative painkiller consumption (as the amount of ibuprofen intake after surgery) was analyzed in two,^{5,41} and lastly, a comparison of the surgical chair time (measured from the end of the local anesthesia placement until the completion of the suture) was made in

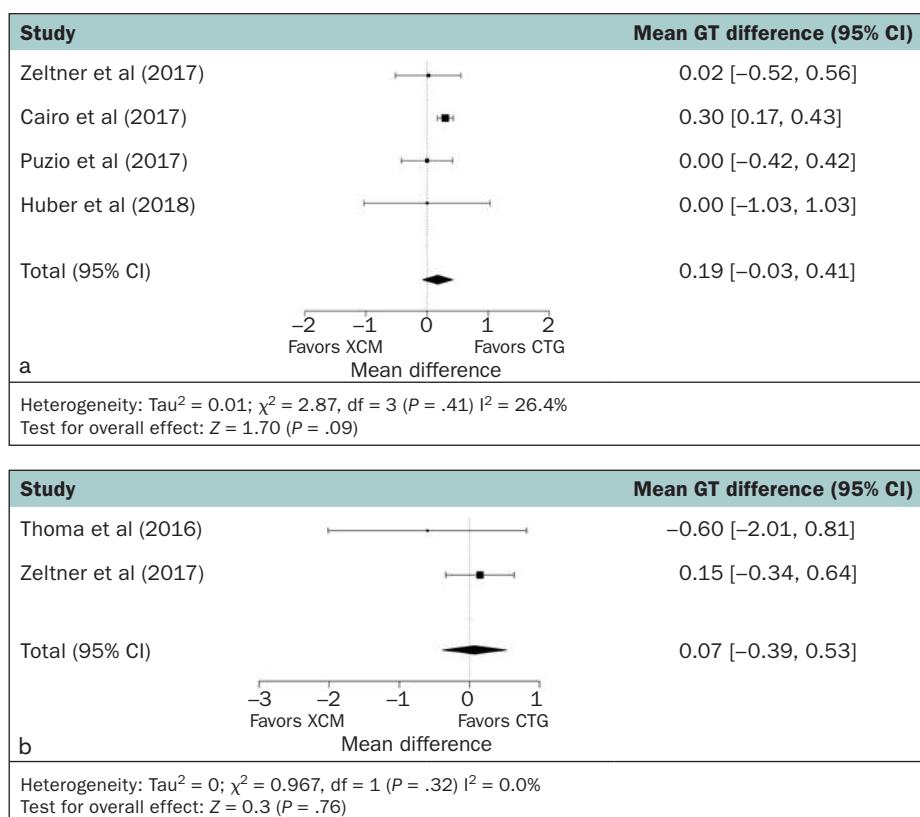


Fig 2 Forest plots of meta-analysis investigating the difference in (a) buccal and (b) crestal gingival thickness (GT) among both treatment groups. CTG = connective tissue graft; XCM = xenogeneic collagen matrix.

three randomized clinical trials.^{5,39,41} The two studies of Thoma et al⁷ and Huber et al³⁸ were based upon the same pool of patients; however, as different outcomes were investigated in both studies, the outcome measures of increase in crestal mucosal thickness and postoperative morbidity reported by Thoma et al⁷ and buccal mucosal thickness and keratinized mucosa width reported in Huber et al³⁸ were included for the meta-analysis.

Increase in Buccal Mucosal Thickness

The increase of buccal mucosal thickness between the connective tissue graft and collagen matrix treatment groups yielded a difference of 0.19 mm (95% CI [−0.03, 0.41]) in favor of connective tissue graft without statistical significance ($P = .09$) (Fig 2a). Heterogeneity as demonstrated by funnel plots (Appendix Fig 1; see online version of this article at quintpub.com) was low ($I^2 = 26\%$, $P = .41$).

Increase in Crestal Mucosal Thickness

Based on the two trials that reported this outcome, increase in mucosal thickness on the crestal site did not differ significantly between the two treatment groups. The estimated difference between the connective tissue graft and collagen matrix was 0.07 mm (95% CI [−0.39, 0.53]) (Fig 2b). This comparison yielded a low

heterogeneity ($I^2 = 0\%$, $P = .3$) as shown in the funnel plots (Appendix Fig 1).

Keratinized Mucosa Gain

The difference in overall keratinized mucosa gain between the two treatment groups was −0.06 mm (95% CI [−30.0, 0.18]), without statistical significance ($P = .62$) (Fig 3). As displayed by the forest plots, subanalyses were performed for trials utilizing the apically positioned flap-based^{39,41} and bilaminar techniques.^{5,7,38,40,42} Both comparisons yielded an insignificant difference of 0.07 mm (95% CI [−0.61, 0.75]), ($P = .84$), and −0.08 mm (95% CI [−0.34, 0.18]), ($P = .53$), respectively. As demonstrated by funnel plots, low heterogeneity was visible for the overall comparison ($I^2 = 0\%$, $P = .86$), and for each subgroup analysis as well ($I^2 = 0\%$, $P = .92$ for the apically positioned flap-based trials; and $I^2 = 0\%$, $P = .45$ for the bilaminar group) (Appendix Fig 1).

Difference in Postoperative Morbidity

The difference in postsurgical discomfort (based on the visual analog scale [VAS]) between the connective tissue graft and xenogeneic collagen matrix groups differed significantly. The estimated difference in VAS reporting was 1.98 (95% CI [0.63, 3.33]), ($P = .004$) in favor of the collagen matrix group (Fig 4a). Moderate

Fig 3 Forest plots of meta-analysis comparing the difference in keratinized mucosa (KT) gain in the bilaminar and apically positioned flap-based treatment groups. CTG = connective tissue graft; XCM = xenogeneic collagen matrix.

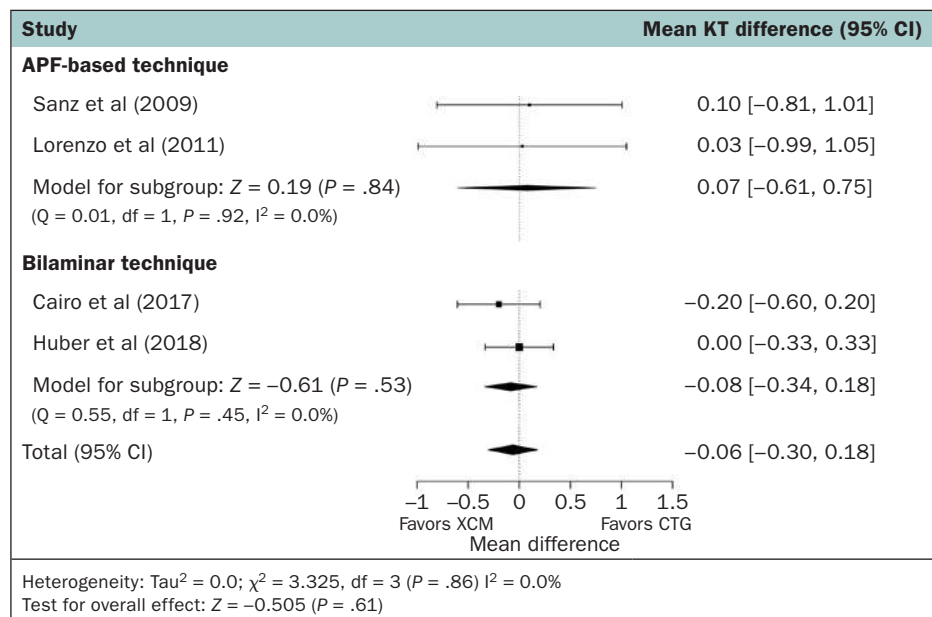
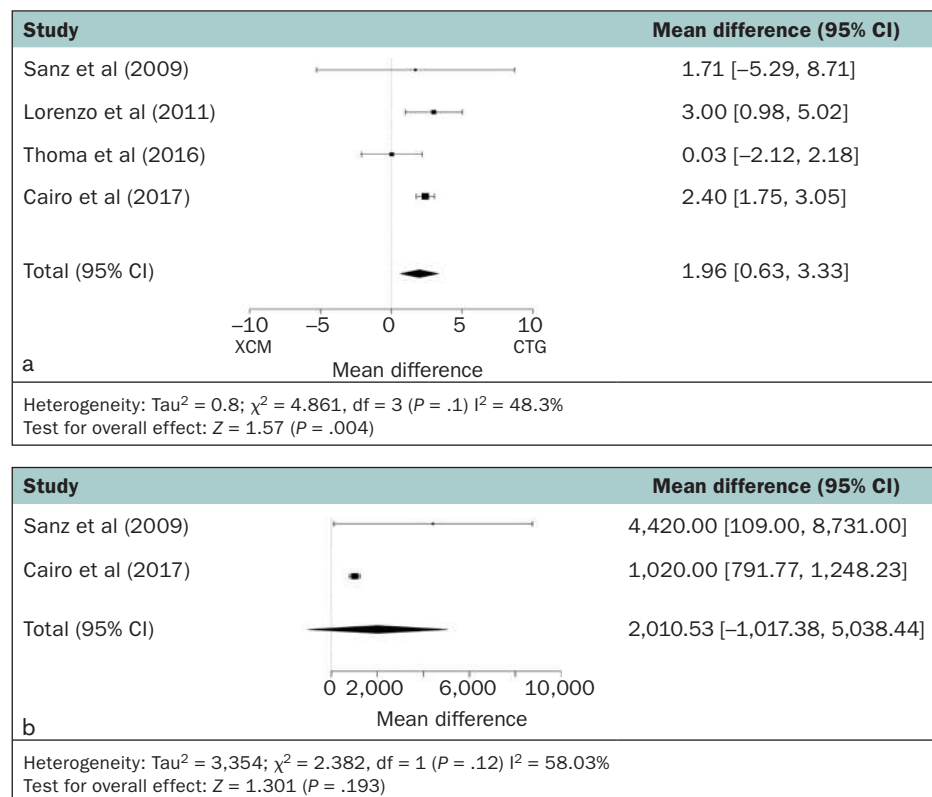


Fig 4 Forest plots displaying the results of meta-analysis comparing the difference in (a) postoperative pain and (b) painkiller consumption among the two groups. CTG = connective tissue graft, XCM = xenogeneic collagen matrix.



heterogeneity, as displayed in the funnel plot, was observed for this comparison ($I^2 = 48.3\%$, $P = .18$) (Appendix Fig 1).

Two randomized clinical trials reported on the amount of painkiller consumption (ibuprofen) of patients after the surgical procedures in both the connective tissue graft and collagen matrix groups.^{5,41}

The difference in pain medication intake was estimated at 2,010.53 mg (95% CI [-1,017.38, 5,038.44]) additional ibuprofen intake in the groups treated with connective tissue graft (Fig 4b). This difference, however, lacked statistical significance ($P = .1$), and substantial heterogeneity was observed ($I^2 = 58\%$, $P = .1$) (Appendix Fig 1).

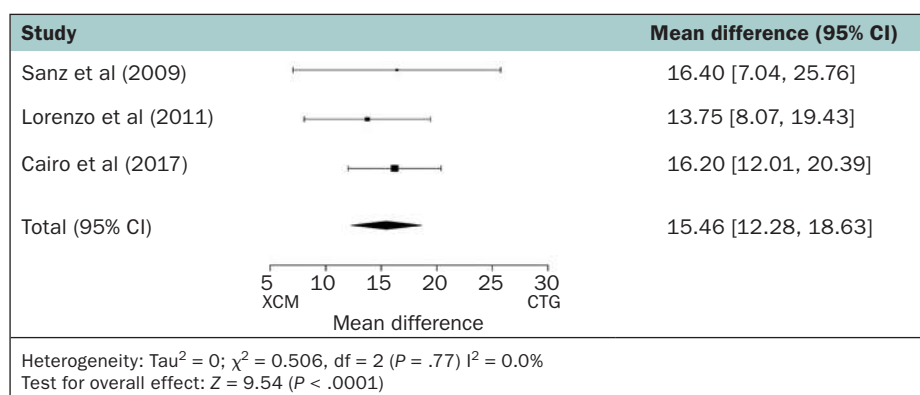


Fig 5 Forest plot of the meta-analysis comparing the surgical chair time recorded (in minutes). CTG = connective tissue graft; XCM = xenogeneic collagen matrix.

Difference in Chair Time

The evaluation of surgical chair time revealed a significant difference between the connective tissue graft and collagen matrix groups. A significantly reduced treatment time of 15.46 minutes (95% CI [12.28, 18.63]; $P < .001$) was associated with the collagen matrix treatment group (Fig 5). This comparison revealed a low heterogeneity ($I^2 = 0\%$, $P = .77$) as registered by the funnel plot (Appendix Fig 1).

DISCUSSION

Principal Findings

The importance of having a thick peri-implant mucosa is not only related to volume compensation of deficiencies¹ and higher marginal bone stability,^{2,3} but also to the possibility of masking the grayish color of the metal abutment.^{4,9} The results of the present review have demonstrated that collagen matrix was as effective as connective tissue graft in increasing peri-implant mucosal thickness. In an experimental study, Thoma et al (2017) reported a favorable integration of both collagen matrix and connective tissue graft following soft tissue augmentation at implant sites with comparable mucosal thickness gain after 2 months; however, significant remodeling and degradation was observed at 6 months for both grafts.⁴³ Recent randomized clinical trials demonstrated the effectiveness of collagen matrix in increasing tissue thickness, with either slightly less⁵ or comparable⁷ results to connective tissue graft. This difference may be attributed to the type of collagen matrix used (a double layer first generation collagen matrix,⁵ or a second generation of three-dimensionally stable collagen matrix).⁷ Indeed, Thoma et al reported a mucosal thickness increase of up to 1.6 mm without significant differences between collagen matrix and connective tissue graft,⁷ while Cairo et al found a mean increase of 1.2 mm for connective tissue graft and 0.9 mm for collagen matrix.⁵

Nevertheless, both studies concluded that collagen matrix may be a viable substitute to connective tissue graft in augmenting peri-implant soft tissue volume, especially when reducing patient morbidity is the primary concern.^{5,7}

It has been suggested that a competent band of keratinized mucosa (of at least 2 mm) can positively affect the peri-implant health by establishing a seal around the implant,⁹ leading to decreased tissue inflammation and plaque accumulation along with improved oral hygiene for the patient.^{16,44} Implants in the posterior areas, in particular, seem to greatly benefit from the presence of an adequate keratinized mucosa.⁴⁵ In addition, a minimal (< 2 mm) or a lack of keratinized mucosa has been identified as a risk factor for developing peri-implantitis.^{46,47}

The results of the present study showed that collagen matrix might be as effective as a connective tissue graft for increasing the keratinized mucosa. Sanz et al were the first group to report a similar effect with collagen matrix.⁴¹ They suggested that collagen matrix may act as a scaffold, promoting the colonization of fibroblast, blood vessels, and epithelium that eventually contribute to the keratinization of the superficial tissue.⁴¹ Thoma et al reported a well-integrated collagen matrix, histologically, to the surrounding tissues.^{7,48} Cairo et al⁵ further stated that collagen matrix could benefit from a split-thickness flap preparation due to the increased blood supply. Furthermore, Jepsen et al showed that collagen matrix combined with a coronally advanced flap was able to obtain almost twofold keratinized mucosa gain compared with the coronally advanced flap alone in the treatment of localized gingival recessions.⁴⁹

Despite different proposed protocols for minimizing the postoperative pain following palatal harvesting,^{50–52} there is no doubt that using a nonautogenous graft avoids a second surgical site, and is therefore less invasive, faster, and a more tolerable procedure for the patient. Indeed, palatal harvesting is believed to

be the main cause for postoperative morbidity following soft tissue surgery,⁵³ which can affect the patient's perception of the treatment as well.⁵⁴ In addition, intraoperative and postoperative bleeding along with transient numbing of the palatal donor site are possible complications related to harvesting a connective tissue graft.^{23,24} The results of this study showed that collagen matrix had significantly less surgical chair time, patient morbidity, and painkiller consumption. This is in line with previous studies demonstrating longer surgical time and higher postoperative discomfort following connective tissue graft-based root coverage procedures.^{55,56}

Agreements and Disagreements with Previous Studies

The systematic review by Thoma and colleagues aiming at investigating the most effective procedure in increasing keratinized mucosa width and soft tissue thickness around implants concluded that autogenous soft tissue grafts in combination with an apically positioned flap lead in superior results, in terms of Gingival Index improvement and marginal bone levels, compared with the apically positioned flap alone, apically positioned flap + collagen matrix, and control (no treatment).⁹ In addition, the authors stated that mucosal augmentation with autogenous soft tissue grafts was related to significantly less marginal bone loss. However, only one study³⁹ investigating collagen matrix was included in the meta-analysis of Thoma et al for the evaluation of the keratinized mucosa, while no study using collagen matrix was selected when assessing the mucosal thickness.⁹ Nevertheless, given the advantages demonstrated by Thoma and coworkers favoring autogenous soft tissue grafts for peri-implant mucosal thickness and keratinized mucosa width augmentation,⁹ it may be assumed that the same results can also be achieved by using xenogeneic collagen matrices. This is in line with the results obtained from the present meta-analysis.

Clinical Implications

The findings from the present systematic review and meta-analysis suggest that xenogeneic collagen matrix is equally effective to connective tissue graft in increasing mucosal thickness and keratinized mucosa width at implant sites, but with significantly lower patient morbidity.

Limitations

The limitation of this systematic review can be due to a rather small number ($n = 7$) of randomized clinical trials available that compare xenogeneic collagen matrix to connective tissue graft in soft tissue augmentation

at implant sites. However, the authors of the present review believe that their decision to only include randomized clinical trials instead of increasing the sample size with controlled trials, retrospective studies, or case series as previously performed in past reviews, greatly increases the quality of this paper and significantly reduces unwanted and potential bias.^{9,57} The present study included both generations of xenogeneic collagen matrices, which introduced some heterogeneity to the results, although similar results were eventually found. In addition, five included trials were performed with a bilaminar technique,^{5,7,38,40,42} and the remaining studies used apically positioned flap approaches.^{39,41} The different surgical approaches might also contribute to some heterogeneity. Additionally, not all soft tissue augmentations were performed at the same time points. However, a recent systematic review and meta-analysis failed to reveal a significant difference for the timing of augmentation for peri-implant soft tissues.⁵⁸ Furthermore, due to the short-term available data, a comparison of the two treatments regarding implant marginal bone loss after soft tissue augmentation was not feasible. Lastly, the randomized clinical trials included in the present meta-analysis were supported by the company that produces the xenogeneic collagen matrix, and therefore, the results should be interpreted with caution.

Recommendations for Future Research

Recommendations for future research are as follows:

- Increase the number of randomized clinical trials evaluating the outcomes of peri-implant mucosal thickness and keratinized mucosa width augmentation using xenogeneic collagen matrix or connective tissue graft
- Randomized clinical trials including patient-related outcomes
- Randomized clinical trials with longer follow-up also evaluating the peri-implant marginal bone level changes over time
- Randomized clinical trials that follow the CONSORT guidelines

CONCLUSIONS

This meta-analysis based on seven randomized clinical trials suggests that the use of collagen matrix is equally effective to the connective tissue graft in increasing peri-implant soft tissue thickness and keratinized mucosa. Nevertheless, further studies will be required to evaluate the long-term effectiveness of collagen matrix-based soft tissue augmentation on peri-implant marginal bone stability.

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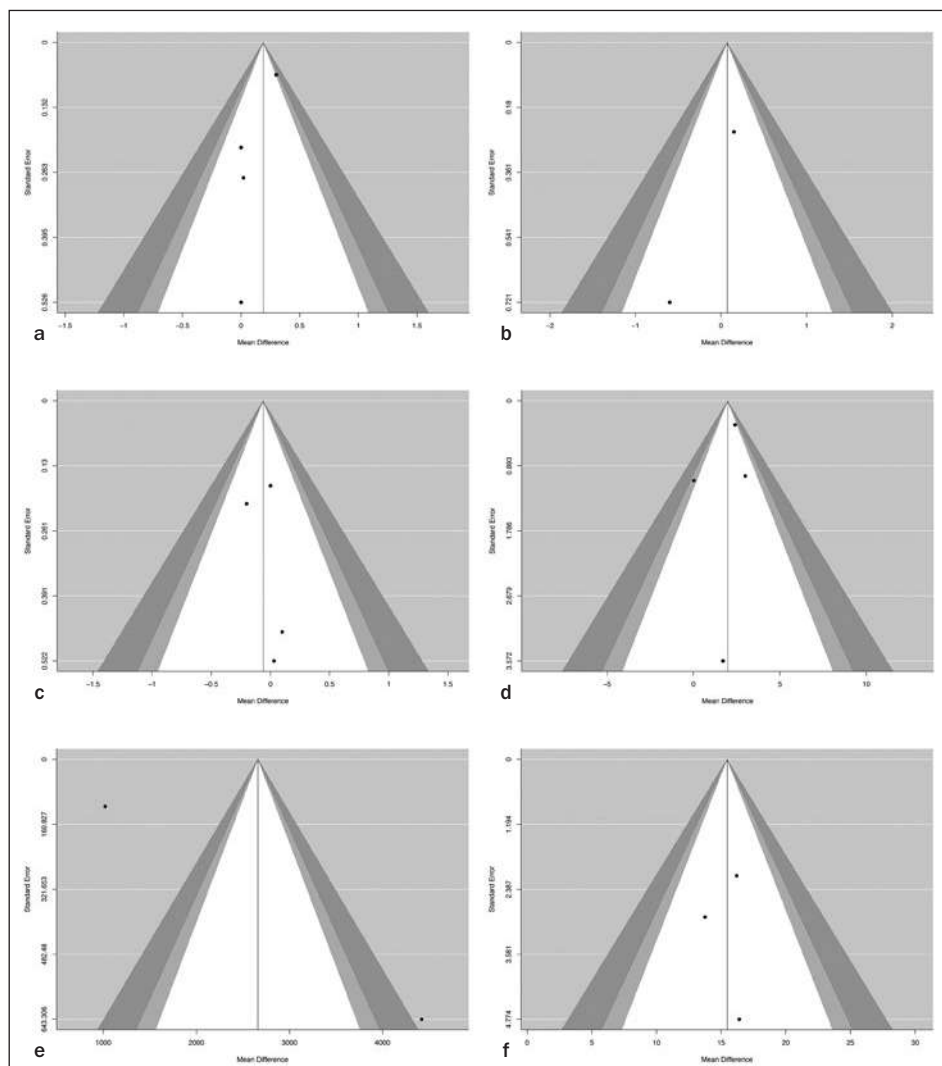
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APPENDIX

Appendix Table 1 Bias Risk Assessment for the Included Randomized Clinical Trials Using The Cochrane Risk of Bias Tool for Randomized Controlled Trials⁵⁹

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addresses	Selective reporting	Other bias	Overall risk of bias
Sanz et al ⁴¹ (2009)	Low	Low	Low	Low	Low	Low	Low	Low
Lorenzo et al ³⁹ (2011)	Low	Low	Low	Low	Low	Low	Low	Low
Thoma et al ⁷ (2016)	Low	Low	Low	Low	Moderate	Moderate	Low	Moderate
Zeltner et al ⁴² (2017)	Low	Low	Moderate	Moderate	Low	Low	Low	Low
Cairo et al ⁵ (2017)	Low	Low	Low	Low	Low	Low	Low	Low
Puzio et al ⁴⁰ (2017)	Low	Low	Low	Low	Low	Low	Low	Low
Huber et al ³⁸ (2018)	Low	Low	Low	Low	Low	Low	Low	Low

**Appendix Fig 1** Funnel plots investigating potential publication bias and heterogeneity among the performed meta-analytic comparisons for the outcomes of: (a) buccal mucosal thickness increase; (b) crestal mucosal thickness increase; (c) keratinized tissue gain; (d) postoperative morbidity; (e) painkiller intake; and (f) chair time difference.

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