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SYSTEMATIC REVIEWS AND META-ANALYSIS

Surgical procedures for soft tissue augmentation at implant sites. A systematic review and meta-analysis of randomized controlled trials

Francesco Cairo DDS[1] | Luigi Barbato DDS[1] | Filippo Selvaggi DDS[1] | Maria G. Baielli DDS[1] | Adriano Piattelli MD, DDS[2,3,4] | Leandro Chambrone DDS[5,6]

[1]Research Unit in Periodontology and Periodontal Medicine, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

[2]Department of Medical, Oral and Biotechnological Sciences, G. D'Annunzio University of Chieti-Pescara, Chieti, Italy

[3]Chair of Biomaterials Engineering, Catholic University of San Antonio of Murcia (UCAM), Murcia, Spain

[4]Villaserena Foundation for Research, Città Sant'Angelo, Pescara, Italy

[5]School of Dentistry, Ibirapuera University (Unib), São Paulo, Brazil

[6]Unit of Basic Oral Investigation (UIBO), School of Dentistry, El Bosque University, Bogota, Colombia

Correspondence
Dr. Francesco Cairo, Research Unit in Periodontology and Periodontal Medicine, Department of Experimental and Clinical Medicine, University of Florence, via fra' Giovanni Angelico 51, 50121 Firenze, Italy.
Email: cairofrancesco@virgilio.it

Abstract

Background: Different procedures were proposed to augment soft tissue around dental implants.

Objective: Aims of this Systematic Review (SR) were to evaluate (a) clinical benefit of soft tissue augmentation at implant sites (b) which is the best surgical procedure to augment soft tissue.

Materials and Methods: Manual/electronic searches were performed to identify randomized controlled trials (RCTs). Change in keratinized tissue thickness (STT) and height (KT) were primary outcomes. Random effects meta-analyses were performed where suitable and expressed as weighted mean differences (MD) with their associated 95% confidence intervals (CI).

Results: Fourteen RCTs accounting for 475 patients and 538 implants were included. Only five studies were judged at low risk of bias. In the single studies, soft augmentation lead to higher STT and KT compared to no augmentation. Considering primary outcomes, connective tissue graft (CTG) was more effective than xenogeneic collagen matrix (XCM) to improve STT (MD: −0.30 mm; 95% CI −0.43; −0.17; $P < .00001$) in the meta-analysis for different techniques for augmentation.

Conclusions: Even if further studies at low risk of bias are needed, soft tissue augmentation techniques improved quantity and quality of peri-implant soft tissue. Among the augmentation procedures, CTG was associated to higher STT change compared to XCM.

KEYWORDS

implant, soft tissue grafting, systematic review

1 | INTRODUCTION

Buccal keratinized tissue (KT) around dental implants might be critical to prevent peri-implant inflammation.[1-3] Furthermore, soft tissue appearance, along with crown form, is associated with patient satisfaction.[4] Preclinical studies suggested also that absence of peri-implant KT is associated with higher susceptibility to plaque-induced inflammation.[5] Several techniques for improving peri-implant soft tissue have been proposed, including pedicle flaps and soft tissue grafts.[6] Recently, the use of dermal substitutes was also described.[7,8]

An early systematic review of RCTs focused on soft tissue management at implant sites concluded that there was limited evidence to provide possible recommendations concerning flap design or augmentation techniques at implant site.[9] More recent reviews, reported that apical positioned flap alone or in combination with connective tissue graft or free gingival graft or collagen matrix was effective to augment soft tissue volume.[10,11]

The two focused questions of this systematic review were: "*What is the clinical benefits of soft tissue augmentation procedure at implant sites in terms of thickness and height of keratinized tissue?*" and "*Which is the best surgical procedure to augment soft tissue?*"

2 | MATERIALS AND METHODS

2.1 | Protocol development and eligibility criteria

A detailed review protocol was written according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement for reporting systematic reviews and meta-analyses.[12,13]

2.2 | Study selection

Only RCTs treating at least 10 patients per group, with at least 3 month-follow-up and published in English language were considered. The inclusion criteria were organized by the PICO method as follows:

(P) Population: Patients requiring soft tissue augmentation at implant site to augment keratinized tissue height/thickness for aesthetic purpose and/or functional reasons.

(I) Interventions: Any type of surgical procedures to augment soft tissue at implant site.

(C) Comparisons: (focused question 1) between a soft tissue augmentation procedure around dental implants vs no augmentation procedure; (focused question 2) any type of comparison between different techniques for soft tissue augmentation around dental implants including grafts or biomaterials.

Additionally, included studies were grouped into three possible clusters for both focused questions:

1. soft tissue augmentation before prosthetic treatment;
2. soft tissue augmentation after prosthetic treatment;
3. soft tissue augmentation at immediate implant placement.

(O) Type of outcome measures: Primary outcome were changes in keratinized tissue thickness (STT) and keratinized tissue height (KT). Secondary outcomes were implant survival (IS), marginal bone level (MBL) variation, aesthetic evaluation, patient satisfaction, and complications.

2.3 | Information source and study selection

Two reviewers (LB, FS) conducted the electronic search on three online databases:

1. The National Library of Medicine (MEDLINE by PubMed);
2. The Cochrane Oral Health Group Trials Register;
3. EMBASE.

Last update was on April 30th 2019. A detailed description is reported in the section "search strategy."

The hand search was conducted on the following journals covering from 2000 to April 2019: *Journal of Clinical Periodontology*, *Journal of Periodontology*, *International Journal of Periodontology and Restorative Dentistry*, *European Journal of Oral Implantology*, *Journal of Oral Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, and *Clinical Oral Implants Research*. References from previous SRs were also checked.

2.4 | Outcomes measures

Primary outcome: changes in STT and KT in mm or percentages.

Secondary outcomes:

- IS considered as presence of loaded and stable implant regardless prosthetic and peri-implant conditions or patient satisfaction;
- MBL measured on intraoral radiographs taken with the paralleling technique;
- Complications (Comp) intended as any biological, prosthetic or mechanical complications, including infections, dental injuries after implant placement, neurosensory impairments;
- Professional evaluation of aesthetic outcomes (Aesth) using standardized approaches, including index as PES (pink aesthetic score), WES (white aesthetic score) or questionnaire evaluations including Visual Analogue Scale (VAS).
- Patient aesthetic assessment and overall satisfaction (Sat) measurements evaluated by questionnaire including VAS.

2.5 | Data collection process

Two review authors (MGB, LB) screened titles and abstracts. Disagreements were solved by discussion with a third reviewer (FC). Eligibility process was conducted on full texts and articles not fulfilling the inclusion criteria were excluded. Authors were contacted to clarify any doubts. Data were extracted using specifically designed data-collection forms. According to the focused questions, it was planned to divide trials in studies comparing augmentation vs no augmentation or different augmentation techniques.

2.6 | Risk of bias in individual studies

The tool for assessing risk of bias of Cochrane Handbook for Systematic Reviews of Interventions was used. Briefly, seven domains (sequence generation, allocation concealment, blinding of the outcome assessor, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other bias) were considered and included in a specific table.

Risk of bias in the included studies was categorized as below:

1. Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
2. Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partly met.
3. High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

2.7 | Quantitative data synthesis

Data were organized into evidence tables and grouped according to type of intervention in order to provide a summary of individual studies characteristics and estimate the possibility of further synthesis methods (ie, meta-analysis). Random-effects meta-analyses for continuous outcomes were used throughout and pooled estimate were expressed as weighted mean differences (MD) with their associated 95% confidence intervals (CI). The analyses were conducted using the generic inverse variance statistical method where the MDs and SEs were entered for all studies to allow the combination of parallel and split-mouth group studies. For split-mouth trials it was assumed an intracluster correlation coefficient of .05, while for parallel trials a coefficient of 0 for the calculation of SE. The significance of any discrepancies in the estimates of the treatment effects from different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistic. In addition, individual studies' data were included into the meta-analyses as subgroups according to the follow-up.

2.8 | Evaluation of the strength of evidence

Evidence regarding provided by RTCs was rated using different levels of methodological strength modified from GRADE (grading of recommendations assessments development and evaluation).[14] Three different strength of evidence were considered:

- High: At least three RCTs at low risk of bias and low heterogeneity
- Moderate: More than one RCT and at least one RCT at low risk of bias, low I^2
- Low: Lack of RCTs or RCTs at high risk of bias or high heterogeneity

3 | RESULTS

3.1 | Study selection

Search results were presented in Figure 1. The electronic search provided a total of 3457 articles and 2108 remained after duplicates removal. The hand search provided 11 additional articles for a total of 2119 studies. After screening of title and abstract, 32 articles were selected. Eighteen articles were excluded since not meeting inclusion criteria. Finally, 14 RCTs were included in the SR. Reasons for exclusion is reported in Table 1. No included RCT showed a follow-up longer than 2 years.

3.2 | Study characteristics

Different surgical procedures for soft tissue augmentation at implant sites were described in the included studies accounting for 475 patients and 538 implants.

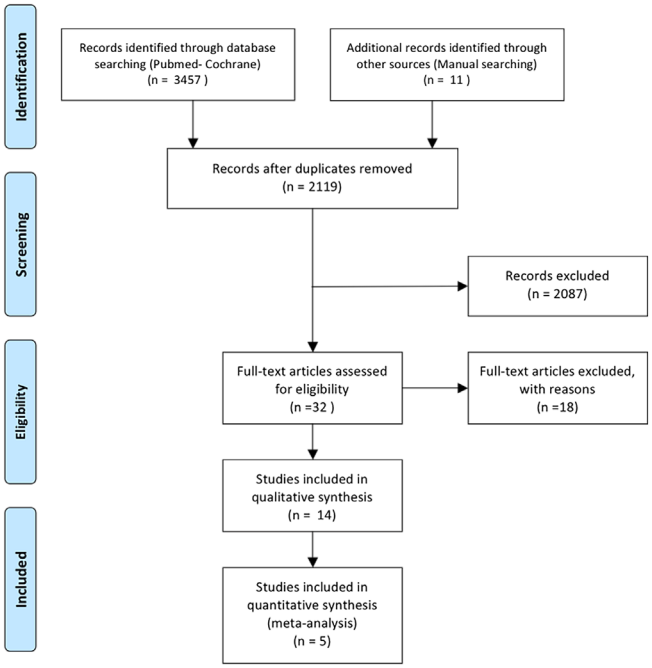

FIGURE 1 PRISMA flow diagram for studies inclusion process

3.3 | Risk of bias within studies

Only five studies were considered at low risk of bias,[33-37] four were at unclear risk,[38-41] and five studies were considered at high risk of bias[7,8,42-44] (Figure 2).

3.4 | Results of individual studies

Studies comparing augmentation procedure vs no augmentation.

1A. Soft tissue augmentation before prosthetic treatment: augmentation vs *no augmentation* (three two studies including 68 patients for a total of 78 implants).

- Wiesner et al treated 10 patients in a split-mouth RCT for a total of 20 implants (10 test + 10 control). One side received a CTG, while the other side had no augmentation. Similar results for changes in MBL were reported after 12 months (−0.79 mm ± 0.30 test group vs −0.62 mm ± 0.38 control group). The CTG group showed better result for change in STT (1.20 mm ± 0.63 test vs −0.15 mm ± 0.34 control; $P < .001$). This study was considered at unclear risk of bias.[37]
- Froum et al tested a Xenogeneic Collagen Matrix (XCM) (test) vs flap alone (control) in 31 patients (17 test group and 14 control group). After 3 months, a significant difference favoring XCM for STT change (0.74 mm ± 0.78 test vs 0.09 mm ± 0.40 control; $P = .009$) while similar results for KT change (0.17 mm ± 1.81 test vs 0.86 ± 1.31 mm; $P = .250$) were reported. This study was considered at high risk of bias.[38]
- Zafiropoulos et al compared a XCM (test) vs flap alone (control) recruiting 38 patients but reporting data only of 27 patients (14 test and 13 control). STT changes favored the XCM group measured

TABLE 1 Excluded studies with reasons

Reason for exclusion	Articles
Not RCT	Speroni et al[15]; Schmitt et al[16]; Frisch et al[17]; Linkevicius et al[18]; Puisys et al[19]; Rungcharassaeng et al[20]; Stimmelmayr et al[21]; Zafiropolous et al[22]; Thoma et al [23]
Not RCT	Buyukozdemir Askin et al,[24] Vellis et al[25]
Unclear randomization procedure	Puzio et al[26]
Not in English language	Lai et al[27]; Liu et al[28]
Data on teeth and implants	Sanz et al[29]
All test and control sites were treated with ridge preservation at the time of extraction using bone graft and a thick soft tissue graft from tuber maxilla.	Zuiderveld et al[30]
Less than 10 patients for group	Anderson et al[31]; Temmerman et al[32]

both at 1 mm (1.06 mm; 95% CI 0.95 to 1.17 test vs 0.02 mm 95% CI −0.04 to 0.08 control; $P < .001$) and 3 mm (0.89 mm 95% CI 0.80 to 0.98 test vs −0.05 mm 95% CI −0.21 to 0.11 control; $P < .001$) from the gingival margin after 6 months. This study was considered at high risk of bias.[44]

1B Soft tissue augmentation after prosthetic treatment: augmentation vs no augmentation (one study including 28 patients with 41 implants)

- Oh et al tested Free Gingival Graft (FGG) + oral prophylaxis (test) vs oral prophylaxis alone (control) in 28 patients (14 test and 14 control) for a total of 41 implants (21 test and 20 control). After 18 months, the FGG group obtained better results for KT change (2.78 mm ± 1.85 test vs 0.38 mm ± 0.56 control; $P = .005$) and MBL changes (0.03 mm ± 0.06 test vs 0.31 mm ± 0.10 control; $P < .05$ for both mesial and distal measurements' comparisons). This study was considered at unclear risk of bias.[41]

1C Soft tissue augmentation at postextraction implant placement: augmentation vs no augmentation (three studies including 126 patients for 126 implants)

- Yoshino et al compared CTG + Immediate Implant Placement and Provisionalization (IIPP) (test) vs the IIPP alone (control) in 20 patients for 20 implants (10 group test and 10 control group). Demineralized bovine bone was used to fill gap between implant and cortical bone in both groups. After 12 months, there was no difference between groups for MBL changes (−0.1 mm ± 0.27 test vs −0.14 mm ± 0.53 control; $P = .76$). This study was considered at unclear risk of bias.[42]
- Migliorati et al tested the CTG + IIPP (test) vs IIPP alone (control) in 48 patients with 48 implants (24 for group). Demineralized bovine bone was used to fill the gap between implant and cortical bone in both groups. Similar outcomes for MBL (0.125 ± 0.076 test vs −0.025 ± 0.08 control) and for KT change (−10% ± 6.7 test vs −17.6% ± 9.9 control; $P = .86$) were reported after 24 months, while CTG group showed significant better results for STT change (+34.3% ± 20.8 test vs −9.9% ± 13.8 control; $P < .001$). This study was considered at unclear risk of bias.[40]
- Zuiderveld et al compared the CTG + IIPP (test) vs the IIPP (control) alone in 58 patients for 58 implants (29 for group). The authors used in the test group a CTG harvested from maxillary tuberosity. A mix of demineralized bovine bone and autologous

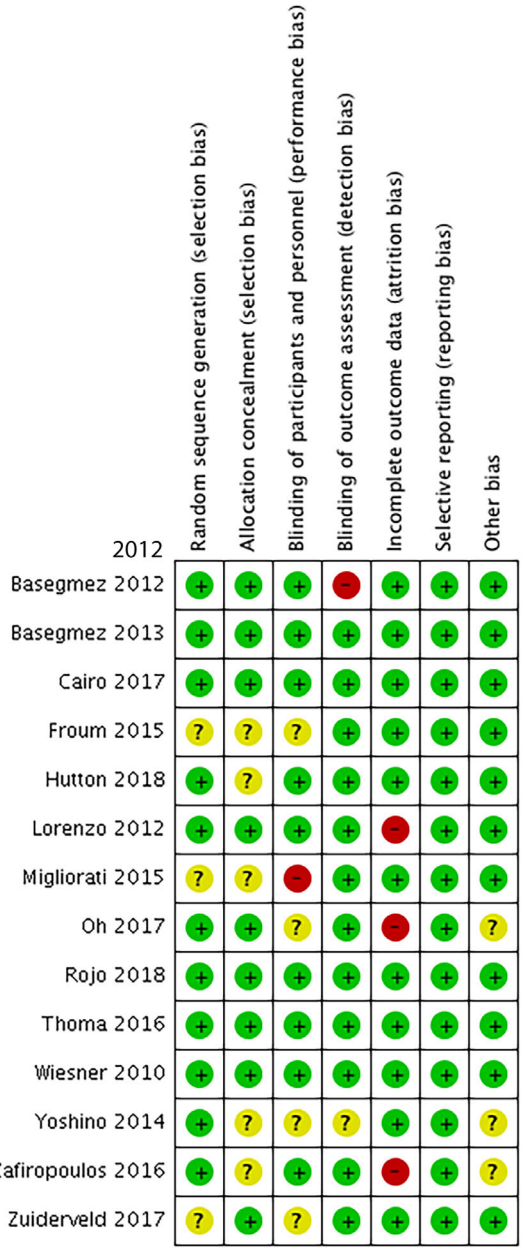

FIGURE 2 Risk of bias summary

bone was used to fill buccal defect in both groups. Twelve months after treatment, similar results were reported for MBL change (−0.03 mm ± 0.41 test vs −0.045 mm ± 0.10 control; *P* value not shown). This study was considered at unclear risks of bias.[43]

Studies comparing different augmentation techniques.

2A Soft tissue augmentation before prosthetic treatment: different augmentation techniques (four studies including 129 patients for a total of 133 implants).

- Thoma et al tested a XCM (test) vs CTG (control) in 20 patients with 20 implants (10 implants in each group). After 3 months, both procedures showed similar results for STT changes measured occlusal (1.4 mm ± 1.4 test vs 0.8 mm ± 1.8 control; $P = .359$), buccal (1.1 mm ± 1.4 test vs 0.8 mm ± 2.2 control; $P = 1.000$) and apical (0.9 mm ± 1.9 test vs 1.6 mm ± 2.6 control; $P = .470$). This study was considered at low risk of bias.[36]
- Cairo et al tested XCM (test group) vs the CTG (control group) in 60 patients (30 patients in each group) at implant uncovering. After 6 months, there were no differences between group for MBL around implants (0.1 mm; 95% CI −0.1 to 0.3; $P = .3022$) and KT change (0.1 mm; 95% CI −0.3 to 0.5). On the other hand, CTG group showed higher STT (−0.3 mm; 95% CI −0.5 to −0.2; $P < .0001$) at the final follow-up. This study was considered at low risk of bias.[34]
- Rojo et al compared the CTG harvested from palate side (control) to CTG from the tuberosity area (test) in 29 patients for a total of 33 implants (15 control group and 18 test group). At 3 months both procedures showed similar outcomes for STT changes (0.69 mm ± 0.23 control vs 0.79 mm ± 0.10 test; $P = .64$) and KT changes (0.87 mm ± 0.99 control vs 1.28 mm ± 0.67 test; $P = .29$). This study was considered at low risk of bias.[35]
- Hutton et al tested CTG (control) vs Acellular Dermal Matrix (ADM) (test) at the time of implant insertion in healed sites (20 patients, 10 implants for each group). After 4 months, there was no difference between groups for KT changes (−0.85 mm ± 1.13 control vs −0.45 mm ± 1.30 test; $P = .539$) and STT changes measured at the different vertical point respect to the free mucosal margin. This study was considered at unclear risk of bias.[39]

2B Soft tissue augmentation after prosthetic treatment: different augmentation techniques (three four studies including 124 patients with 160 implants).

- Başeğmez et al compared an ADM vs the FGG. After 6 months, differences favoring FGG in term of final KT (3.58 mm ± 0.40 vs 2.47 mm ± 0.32; $P < .001$) and KT gain (2.57 mm ± 0.50 vs 1.58 mm ± 0.37; $P < .001$) were found. This study was considered at high risk of bias.[33]
- Başeğmez et al compared the FGG and the vestibuloplasty in 64 patients (64 implants). After 12 months, differences favoring FGG in term of final KT (3.11 mm ± 0.58 test vs 1.83 mm ± 0.73 control; $P < .001$) and KT gain (2.36 mm ± 0.49 test vs 1.15 mm ± 0.81 control; $P < .001$) were found. This study was considered at unclear risk of bias.[7]
- Lorenzo et al treated 24 patients, 12 received a XCM (test) while 12 a CTG (control group). KT change was similar between groups after 6 months (2.30 mm test vs 2.33 control; $P = .58$). This study was considered at high risk of bias.[8]

3.5 | Implant survival rate

Considering studies comparing augmentation vs no augmentation, Zuiderveld et al reported one implant failure in test (CTG) and one in control group (no augmentation) treated with postextraction implants.[43] No implant failure was reported in studies comparing different augmentation procedures.

3.6 | Complications and aesthetic outcomes

Very few complications were reported in enclosed studies, including the need for subgingival curettage in case of mucositis in the study by Oh et al[41] and provisional restoration detachment in Yoshino et al.[42] Furthermore, even if patients were usually described as highly satisfied, standardized approached for professional evaluation were not frequently used thus impairing a possible meta-analysis.

3.7 | Synthesis of results

Due to heterogeneity among selected studies, only five RCTs were included in two meta-analysis. Meta-analysis for STT change or KT change was not possible for studies comparing *augmentation* vs *no augmentation*, while was performed for MBL change at postextractive implants. Twelve months after IIPP with alveolar ridge preservation, the CTG grafted sites showed inferior MBL compared to no augmented sites (two studies, difference −0.10 mm; 95% CI −0.14; −0.06; $P < .00001$, $I^2 = 0\%$)[40,42] (*low strength of evidence*). Similarly, overall estimates including also the trial by Zuiderveld et al, that evaluated MBL between the first and 12th month, identified significant differences between groups (three studies, difference −0.09 mm; 95%CI −0.13; −0.06; $P < .0001$, $I^2 = 0\%$) (Figure 3)[40,42,43] (*low strength of evidence*).

The second meta-analysis was performed for studies dealing on different surgical techniques. This analysis tested the use of XCM vs CTG at implant site before prosthetic treatment considering data from Thoma et al (apical measurements) and from Cairo et al. The outcomes showed a significant difference favoring CTG (difference −0.30 mm; 95% CI −0.43; −0.17; $P < .00001$, $I^2 = 0\%$) for STT (Figure 4)[34,36] (*moderate strength of evidence*).

Although there were two studies testing XCM vs flap alone and both of them reported the results of STT,[38,44] formal data pooling (ie, meta-analysis) was precluded due differences in the reference points (ie, location/area) where the measurements were performed. Froum et al[38] assessed STT "at a point 1 mm coronal to the MGJ", while Zafiropulos et al[44] measured the STT using other two different reference points, one

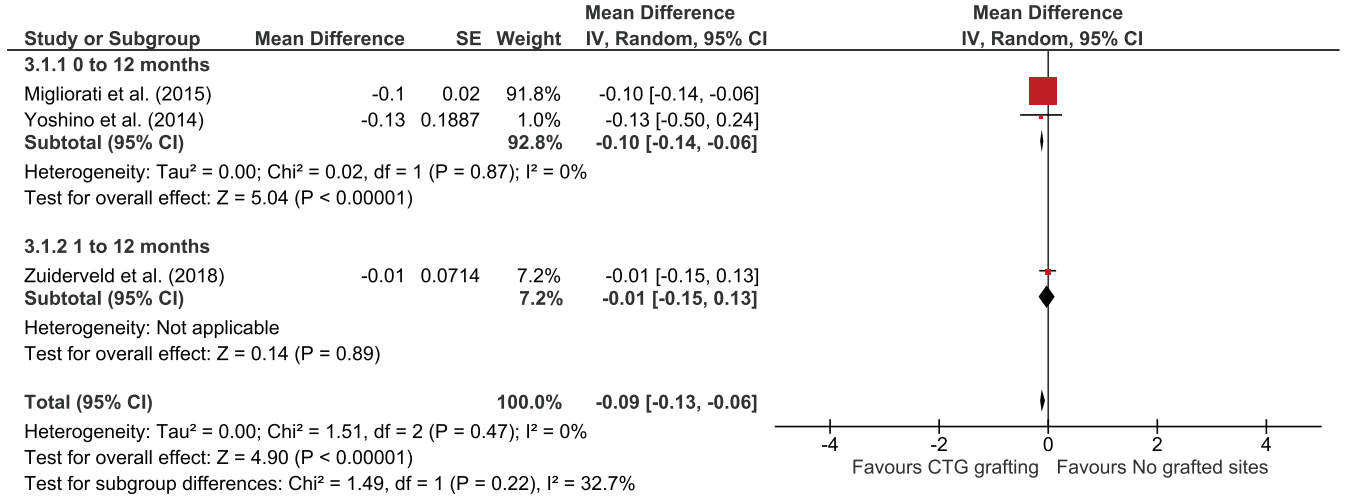

FIGURE 3 Meta-analysis for marginal bone loss (MBL) change comparing augmentation vs no augmentation at postextractive implants (IIPP)

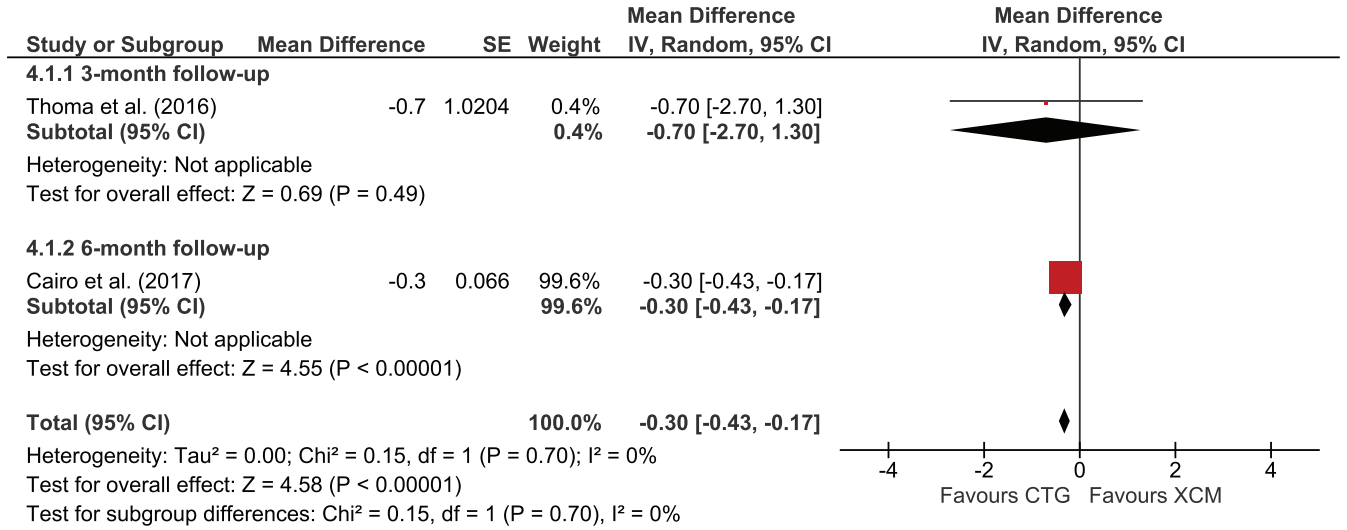

FIGURE 4 Meta-analysis for soft tissue thickness (STT) comparing xenogeneic graft (XCM) vs CTG at headed implant sites

"was positioned 1 mm below the gingival margin (for STT 1 measurement), and the other was positioned 3 mm below the mucogingival margin MGJ."

4 | DISCUSSION

The present systematic review assessed current evidence regarding soft tissue augmentation procedures at implant site. A total of 14 RCTs using different surgical procedures for soft tissue augmentation were included; data on 475 patients and 538 implants were finally available. Interestingly, included RCTs were published between 2010 and 2018, thus confirming that is a modern interest in clinical research.

The first focused question aimed to evaluate the potential clinical benefits in soft tissue augmentation at implant sites comparing reconstructive procedures vs no additional therapy. A total of 7 RCTs for 222 patients and 245 implants were identified. Even if meta-analysis was not possible, clinical data from single studies suggested that soft tissue augmentation provided higher benefits in terms of STT and KT. When considering the subgroup of *soft tissue augmentation after prosthetic treatment*, a single RCT tested adding FGG vs prophylaxis alone at sites with limited amount of keratinized tissue. FGG treated sites showed higher keratinized tissue height (KT), less gingival inflammation and less crestal bone loss (~0.3 mm) than control 18 months after treatment.[41] This observation corroborates information from a retrospective study with 10 years of follow-up, suggesting that FGG may reduce the risk of soft tissue complications in the long term for implants at posterior mandible.[45]

In this SR, a meta-analysis evaluated the potential benefit of soft tissue augmentation on MBL at postextractive implant sites. The reported difference seems to support the potential capability of CTG in improving soft tissue quality and promoting bony healing at extraction sites treated with titanium implants (difference −0.09 mm; 95% CI −0.14; −0.05; $P < .00001$) (Figure 3). Accordingly to GRADE assessment, the present meta-analysis was considered at low strength of evidence.

Interestingly, it should be kept in mind that these studies, along with the use of CTG, applied complex strategies for management of

post extractive sites, using bone grafts and an immediate temporary crown application. Furthermore, it should be considered that relevance of the estimated difference seems to be negligible from a clinical point of view, even the long effect should be addressed in further studies.

The second question of the present systematic review was "*Which is the best surgical procedure to augment soft tissue?*." A total of 253 patients and 293 implants were considered. For studies dealing with *Soft tissue augmentation before prosthetic treatment*, a single meta-analysis comparing XCM vs CTG was performed. The analysis showed that adding a CTG under the flap was more effective in term of final STT than XCM (difference, –0.3 mm, 95% CI –0.43; –0.17; $P < .00001$) (Figure 4). Accordingly to GRADE assessment, the present meta-analysis was considered at moderate strength of evidence. The present outcomes confirm the high capability of CTG in supporting soft tissue reconstruction[46] and corroborate experimental observations suggesting the capability of CTG under flap in promoting wound stability.[47,48] This observation was also confirmed by a pilot RCT, suggesting that CTG was more effective than flap alone in increasing peri-implant soft tissue thickness.[37] On the other hand, single studies applying CTG confirmed higher morbidity in patients experiencing harvesting procedures at palatal site,[34,49,50] thus supporting the growing interest in using different replacement biomaterials instead of CTG. Even if, present data support the superiority of CTG, initial outcomes seem to suggest that collagen matrix may improve soft tissue thickness compared with flap alone leading to ingrowth of blood vessel and subsequent collagen fibers maturation.[34,36] However, it should be kept in mind that outcomes of the present meta-analysis clustered results of short term-studies and information concerning soft tissue stability at medium and long-term follow-up is mandatory.

5 | LIMITATIONS

In interpreting the results of the present systematic review, it should be considered the great heterogeneity in terms of applied techniques in different trials. Furthermore, only 5 out of 14 included studies were rated as at low risk of bias, thus suggesting the need in improving quality of RCTs investigating soft tissue reconstruction at implant site. Finally, it should be taken into account that present evidence reported only short-term data and long-term stability of augmented peri-implant soft tissue is not yet established.

6 | CONCLUSIONS

On the basis of the obtained data it appears that:

1. Soft tissue augmentation at implant sites provided significant increase of peri-implant soft tissue quantity at short-term observation.
2. The add of CTG is associated with improved bone level stability at post extractive implants, even if the magnitude of the benefit seems to be minimal from a clinical stand point.
3. CTG is more effective that XCM to improve peri-implant soft tissue thickness before prosthetic treatment
4. Included RCTs showed short-term follow-ups (up to 2 years) and long-term benefit of soft tissue augmentation at implant site is not yet established
5. Further RCTs should be designed to reduce potential methodological biases, as well as to include both clinical and patient-reported outcomes.

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CONFLICT OF INTEREST

Francesco Cairo reported grant support and/or lecture fees from Geistlich Pharma AG and Straumann. The other authors report no conflict of interest.

ORCID

Francesco Cairo https://orcid.org/0000-0003-3781-1715
Luigi Barbato https://orcid.org/0000-0002-0524-7980
Adriano Piattelli https://orcid.org/0000-0002-6246-8130

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