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REVIEW

Peri-implant soft tissue phenotype modification and its impact on peri-implant health: A systematic review and network meta-analysis

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Abstract

Background: The peri-implant soft tissue phenotype (PSP) encompasses the keratinized mucosa width (KMW), mucosal thickness (MT), and supracrestal tissue height (STH). Numerous approaches to augment soft tissue volume around endosseous dental implants have been investigated. To what extent PSP modification is beneficial for peri-implant health has been subject of debate in the field of implant dentistry. The aim of this systematic review was to analyze the evidence regarding the efficacy of soft tissue augmentation procedures aimed at modifying the PSP and their impact on peri-implant health.

Methods: A comprehensive search was performed to identify clinical studies that involved soft tissue augmentation around dental implants and reported findings on KMW, MT, and/or STH changes. The effect of the intervention on peri-implant health was also assessed. Selected articles were classified based on the general type of surgical approach to increase PSP, either bilaminar or an apically positioned flap (APF) technique. A network meta-analysis including only randomized-controlled trials (RCTs) reporting on PSP outcomes was conducted to assess and compare different techniques.

Results: A total of 52 articles were included in the qualitative analysis, and 23 RCTs were included as part of the network meta-analysis. Sixteen RCTs reported the outcomes of PSP modification therapy with bilaminar techniques, whereas 7 involved the use of APF. The analysis showed that bilaminar techniques in combination with soft tissue grafts (connective tissue graft [CTG], collagen matrix [CM], and acellular dermal matrix [ADM]) resulted in a significant increase in MT compared to non-augmented sites. In particular, CTG and ADM were associated with higher MT gain as compared to CM and non-augmented sites. However, no significant differences in KMW were observed across different bilaminar techniques. PSP modification via a bilaminar approach utilizing either CTG or CM showed beneficial effects on marginal bone level stability. APF-based approaches in combination with free gingival graft (FGG), CTG, CM, or ADM showed a significant KMW gain compared to non-augmented sites. However, compared to APF alone, only FGG exhibited a significantly higher KMW gain. APF with any evaluated soft tissue graft was associated with with

reduction of probing depth, soft tissue dehiscence and plaque index compared to non-augmented sites compared to non-augmented sites. The evidence regarding the effect of PSP modification via APF-based approaches on peri-implant marginal bone loss or preservation is inconclusive.

Conclusions: Bilaminar approach involving CTG or ADM obtained the highest amount of MT gain, whereas APF in combination with FGG was the most effective technique for increasing KMW. KMW augmentation via APF was associated with a significant reduction in probing depth, soft tissue dehiscence and plaque index, regardless of the soft tissue grafting material employed, whereas bilaminar techniques with CTG or CM showed beneficial effects on marginal bone level stability.

KEYWORDS
acellular dermal graft, autogenous grafts, collagen matrix, dental implant, evidence-based dentistry, network meta-analysis, soft tissue augmentation, tissue graft

1 | INTRODUCTION

Dental implants offer a reliable therapeutic option for tooth replacement therapy.[1] However, biological, prosthetic, and esthetic complications are not rare events.[2-4] Tantamount to the widely studied significance of peri-implant bone volume,[5-8] the critical role of peri-implant soft tissue on implant esthetics and health has also been at the center of significant discussion in the last decade.[9-13]

Although several investigators have shown that an insufficient amount of keratinized mucosa width (KMW) around dental implants is associated with more plaque accumulation, tissue inflammation, mucosal recession, and/or attachment loss,[14-19] others have reported conflicting findings.[14,20-23] Recent evidence suggests that deficient zones of KMW (<2 mm), the likelihood of patient discomfort, and suboptimal plaque control increases along with the probability of developing marginal bone loss and bleeding on probing.[17,24] In a cross-sectional study, it was found that reduced KMW is a risk indicator for the severity of peri-implant mucositis.[15] In congruence with this finding, Schwarz et al. concluded that KMW plays a crucial role on the prevention and resolution of peri-implant mucositis.[25] Possessing at least 2 mm of KMW has been shown to act as a protective factor against peri-implant diseases in erratic maintenance compliers.[16] Furthermore, the absence of peri-implant keratinized mucosa has also been linked to lower patient esthetic satisfaction,[26] which highlights the importance of the soft tissue component on peri-implant esthetics.[27-30]

Mucosal thickness (MT) also plays a major role not only on the esthetic outcomes,[31-33] but also on peri-implant health. A thicker MT can also provide greater stability of the mucosal margin than thin MT,[32,34-36] which is fundamental to prevent mucosal recession.[35,37,38] A recent systematic review concluded that MT gained may also promote greater stability of interproximal marginal bone levels.[10]

Based on the classic study by Berglundh & Lindhe,[39] soft tissue thickness has been investigated as one of the critical factors affecting peri-implant marginal bone loss. In a series of investigations by Linkevicius et al., it was demonstrated that a thin peri-implant mucosa, as measured from the bone crest in an apico-coronal direction, also referred to as the supracrestal tissue height (STH), is associated with greater marginal bone loss (MBL) than a thick tissue phenotype. This group also demonstrated that augmenting STH via soft tissue augmentation was an effective strategy to minimize peri-implant bone loss.[40-42] The association between thin STH and higher MBL seems to be particularly true for implants placed at the level of the bone crest.[43]

The performance of different techniques to increase the peri-implant soft tissue phenotype (PSP), which includes KMW, MT, and STH, has been extensively investigated.[44] Historically, autogenous soft tissue grafts (either the free gingival graft [FGG] or connective tissue graft [CTG]) were the first grafting approaches evaluated because of the satisfactory results shown around the natural dentition.[45,46] Nevertheless, patient morbidity and the need for a second surgical site[47,48] motivated the development and application of alternative sources of graft replacements, such as acellular dermal matrix (ADM) or xenogeneic collagen matrix (CM).[46,49,50]

Previous systematic reviews have attempted to investigate the influence of peri-implant soft tissue phenotype (PSP) and its modification (PSPM) on peri-implant

health.[10,18,51,52] However, an important limitation of these reviews is the low number of included randomized clinical trials (RCTs), which resulted in data scarcity and heterogeneity, both of which can render the application of a standard meta-analysis (only comparing two interventions at a time), ineffective, and of limited clinical value.

Therefore, the aim of this systematic review was to assess the efficacy of PSPM therapy in augmenting PSP (in terms of KMW, MT, and STH) and in promoting peri-implant health.

2 | MATERIALS AND METHODS

2.1 | Protocol registration and reporting format

The protocol of the present review was registered and allocated the identification number CRD42019146982 in the PROSPERO database, hosted by the National Institute for Health Research, University of York, Center for Reviews and Dissemination.[53] This manuscript was prepared following the Cochrane Collaboration guidelines[54] and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis Extension statement for systematic reviews incorporating network meta-analyses for health care interventions.[55,56]

2.2 | Objectives

The goal of this review was to address the following focused questions in regard to PSPM around implants:

1) What is the efficacy of different surgical techniques aimed at PSPM, in terms of KTW, MT, and STH?
2) What is the effect of PSPM on measures of peri-implant health[57,58] that include peri-implant probing depth (PD), MBL, and mucosal/gingival index?

2.3 | PICOT question[59]

The following Population, Intervention, Comparison, Outcomes, and Time (PICOT) framework was used to guide the inclusion and exclusion of studies for the abovementioned focused questions:

Population (P): Patients who underwent soft tissue augmentation on at least one dental implant site.

Intervention (I): Surgical treatment for PSPM using autologous soft tissue grafts (FGG or CTG), or substitutes (ADM or CM).

Comparison (C): All possible comparisons among the included interventions were explored, with the inclusion of non-treated sites (if available as a comparative arm of a trial) or non-grafted sites (such as the coronal advancement or apical positioning of mucosal flap alone with a graft or biomaterial).

Outcome (O): Change in the phenotype in terms of KMW, MT or STH. Change in probing depth, MBL, soft tissue dehiscence, plaque index, and mucosal/gingival index.

Time (T): Minimum follow-up of 3 months after the surgical intervention.

2.4 | Inclusion criteria

- Soft tissue augmentation at implant sites using FGG, CTG, ADM or CM
- Prospective interventional human studies
- Evaluation and reporting of clinical outcomes of interest (KMW, MT or STH) over a minimum follow-up period of 3 months.

2.5 | Exclusion criteria

- Retrospective clinical studies, case reports or animal studies
- Inclusion of implants with a diagnosis of peri-implantitis[60]
- Soft tissue augmentation around natural teeth
- Simultaneous hard and soft tissue augmentation. For the quantitative analysis any treatment arm that included bone augmentation was excluded from the analysis.
- Studies recruiting only smoking individuals.

2.6 | Search methods for studies identification

A detailed systematic literature search was conducted using the following electronic data bases: The National Library of Medicine (MEDLINE via PubMed); EMBASE via OVID; the Cochrane Central Register of Controlled Trials; and Latin American & Caribbean Health Sciences Literature (LILACS), Web of Science, and Scopus. For examining unpublished trials, the grey literature, non-profit reports, government research or other materials, were also electronically explored through searching in ClinicalTrial.gov and OpenGrey.[61]

The search strategy was primarily designed for the MEDLINE database with a string of medical subject

headings and free text terms, and then modified appropriately for other databases. No restrictions were set for date of publication, journal or language. The search results were downloaded to a bibliographic database to facilitate duplicate removal and cross-reference checks. Details regarding the search strategy and the development of the search key terms for the databases are brought in the Supplementary Appendix in online Journal of Periodontology. The search was conducted on August 19, 2019.

To ensure a thorough screening process, the electronic search was complemented with a manual search in the following journals: *Journal of Dental Research, Journal of Clinical Periodontology, Journal of Periodontology, Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, The International Journal of Oral & Maxillofacial Implants, Journal of Oral and Maxillofacial Surgery, International Journal of Oral Implantology, Clinical Oral Investigations, and International Journal of Periodontics* and *Restorative Dentistry*. The manual search period was from January 1, 2000 to March 26, 2020. Additionally, reference lists of the retrieved studies for full-text screening and previous reviews in the topic of peri-implant soft tissue (plastic) surgery were screened.[9-12,18,22,51,52,62-68]

2.7 | Data collection and management

Two calibrated examiners (LT and SB) screened the titles and abstracts (if available) of the entries identified in the search, in duplicate and independently. Next, the full text version of all studies that potentially met the eligibility criteria or for which there was insufficient information in the title and abstract to make a decision, were obtained. Any article considered as potentially relevant by at least one of the reviewers was included in the next screening phase. Subsequently, the full-text publications were also evaluated in duplicate and independently by the same review examiners. The examiners were calibrated with the first 10 full-text, consecutive publications. Any disagreement on the eligibility of the studies was resolved through open debate between both reviewers until an agreement was reached or through settlement by an arbiter (HLW). All articles that did not meet the eligibility criteria were excluded and the reasons for exclusion were noted. Inter-examiner agreement following full-text assessment was calculated via kappa statistics.

In the case of multiple publications reporting on the same study or investigating the same cohort at different follow-up intervals (or secondary analysis of the same data), it was decided to pool together all relevant details as a single report with the most comprehensive data for inclusion in the qualitative and quantitative analyses. Disagreement on the inclusion of the studies at any point was resolved in the same manner as previously mentioned.

Two examiners (LT and SB) independently retrieved all relevant information from the included articles using a data extraction sheet specifically designed for this review. At any stage, disagreements between the reviewers were resolved through open discussion and consensus. If a disagreement persisted, a third person (HLW) settled the discussion. Aside from the outcomes of interest (e.g., KMW, MT, and STH), the following study characteristics were retrieved:

- Study design, number of centers, geographic location, setting (university versus private practice), and source of funding
- Population characteristics, age of participants, number of participants and treated sites (baseline/follow-up), singular/multiple treated sites, and follow-up period
- Type of intervention, utilization of soft tissue grafting materials and techniques
- Timing of soft tissue augmentation: whether it was at the time of the implant placement, at second stage or delayed.
- Clinical measurements related to peri-implant soft tissue dehiscence, probing depth, plaque index (PI), gingival index (GI),[69] MBL, at baseline and at every follow-up recall, with their method of measurement, as well as patient-reported outcomes, if available. All values were extracted from the selected publications (mean ± standard deviations [SD]).

If data pertinent to the quantitative analysis were missing or if a study did not provide any information on KMW, MT, and STH, attempts were made to contact the corresponding authors to obtain the necessary data. If the attempts were not successful, and the trial did not provide any data on any of the three outcomes of interest, it was excluded.

2.8 | Quality assessment and risk of bias

The risk of bias for the included studies was assessed independently and in duplicate by two authors (LT and SB). For RCTs, it was performed according to the recommended approach by the Cochrane collaboration group.[54] For non-randomized cohort studies included in the qualitative analysis, the ROBINS-I tool[70] was used to determine the potential risk of bias. For case series, the Joanna Briggs Institute Critical Appraisal tool[71] was utilized for quality assessment (refer to Supplementary Appendix in online *Journal of Periodontology*).

Any disagreement was discussed between the same authors. Another author (HLW) was consulted in case no agreement was reached. However, no study was excluded on the basis of the risk of bias within a study.

2.9 | Quantitative analysis and synthesis of the network meta-analysis

The goal of the quantitative assessment was to evaluate and compare the changes in KMW, MT, and STH, which are the components of the PSP. However, because of a lack of sufficient data on STH from the included RCTs, only quantitative analyses on KMW and MT were conducted.

After evaluating the transitivity assumption underlying network analyses (via the distribution of clinical and methodological variables, such as the trial design/approach, and baseline measures) two sets of network meta-analyses were conducted, based on the utilized approaches among the included RCTs.[72,73] The first analysis was performed using the data from trials reporting the outcomes of interventions involving a bilaminar approach, whereas the second analysis was focused on apically positioned flap (APF)-based procedures. Details pertaining to the construction of the model, its mathematical representation and the utilized fixed- and random-effects are available in the Supplementary Appendix in online *Journal of Periodontology*.

For each approach (whether bilaminar or APF-based), changes in KMW and MT among different treatment arms served as the primary outcome. For the network meta-analysis (NMA) on bilaminar techniques, the four treatment arms of ADM, CM, CTG, and non-augmented sites (as the reference) were considered. Non-augmented sites included sites that received implant therapy or second stage surgery without the addition of soft tissue grafts. For the second NMA on the APF-based approaches, the following treatment arms were assessed: ADM, APF, CM, CTG, FGG, and non-augmented sites that served as the initial reference category. Non-augmented sites for APF-based approaches included sites that underwent implant therapy or implant uncovering without the addition of soft tissue grafts, or sites that were just observed over time without any intervention.

The relationship between changes in KMW, MT, and health-related parameters, such as PI, GI, PD, MBL, and a peri-implant soft tissue dehiscence was evaluated through subgroup analyses and network meta-regression.

Baseline characteristics (such as initial KMW and MT) were accounted for in each model and controlled for according to the treatment approach (single/multiple site treatment). The arms were weighted according the treated sample size. The percentage of smoking individuals was calculated among the study arms (as a continuous variable) and controlled for in the models. The analyses accounted for correlations induced by multi-group studies, by using multivariate distributions. The random-affect variances in the distribution (for heterogeneity) were considered to measure the extent of across-studies and within-comparison variability on the treatment effects. To obtain direct and indirect pairwise comparisons for all treatment arms, different reference levels were set in the models and all contrasts were observed and noted along with their standard errors (converted to confidence intervals), and P values. A P value threshold of 0.05 was set for statistical significance. The results of the pairwise comparisons were presented in tabular form and network plots were produced to display the generated relationships for both sets of NMAs and the included treated arms.

The linearity assumption was tested for all analyses by including quadratic terms, however no evidence of non-linearity was noted. All analyses were performed by an author with experience in biostatistics (SB) using the lme4,[74] lmerTest,[75] dplyr,[76] tidyr,[77] igraph,[78] and ggplot2[79] statistical packages in Rstudio (version 1.2.1335).

3 | RESULTS

3.1 | Search results and study selection

The literature search process is shown in Figure 1. Following removal of duplicates, 1888 records were screened on the basis of titles and abstracts. Full-text assessment was performed for 72 articles. Based on the predetermined inclusion criteria, 52 articles were included in the qualitative analysis.[24,41,80-127] The reason for exclusion of the other 20 articles is presented in detail elsewhere (the reader is referred to the Supplementary Appendix in online *Journal of Periodontology*). Twenty-five, of the 52 articles included in the systematic review that reported an RCT, were considered for the network meta-analysis.[80-83,85,86,88,89,94,96,97,100,101,107,109,110,116-120,122-124,126]
The inter-reviewer reliability in the screening and inclusion process, assessed with Cohen's κ, corresponded to 0.86 and 0.93 for assessment of titles and abstracts and full-text evaluation, respectively.

3.2 | Description of studies

Twenty-five articles were RCTs,[80-83,85,86,88,89,94,96,97,100,101,107,109,110,116-120,122-124,126] 12 were non-randomized studies of interventions,[24,41,93,98,99,105,108,112,113,115,32,127] and 15 were prospective case series.[84,87,90-92,95,102-104,106,111,114,34,121,125]
Because of the lack of reporting of results associated

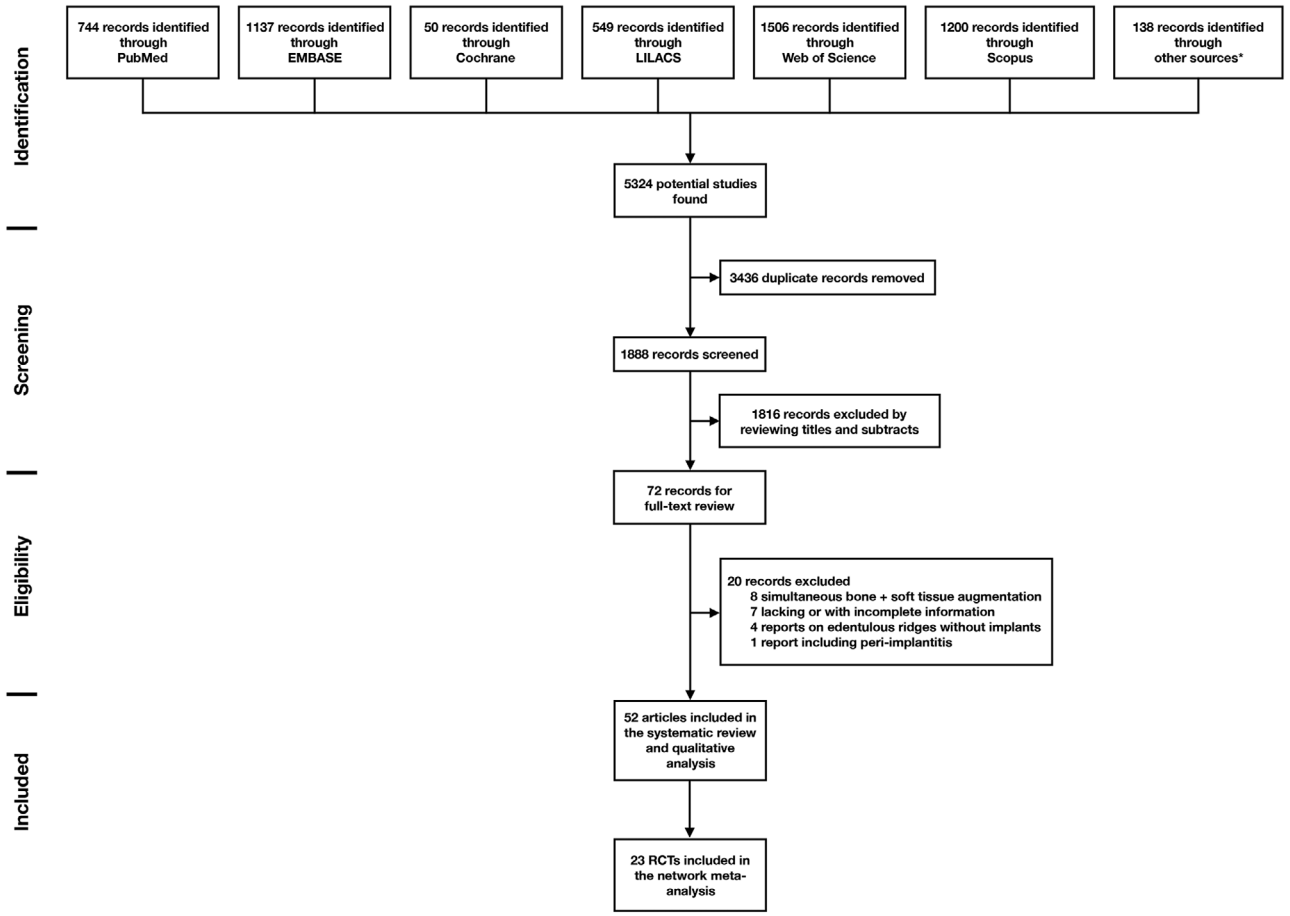

FIGURE 1 The search process and the screening of the articles for identifying the eligible studies. RCT, randomized controlled trial. * refers to search in the grey literature

with PSP outcomes, two RCTs were excluded from the NMA.[83,110] Among the 23 included RCTs in the NMA, 16 trials investigated the outcomes of PSPM using bilaminar techniques[80,86,88,89,94,96,97,107,109,116,118-120,123,124,126] and seven trials did the same with an APF approach.[81,82,85,100,101,117,122] The PSPM outcomes of autogenous grafts versus non-augmented sites were explored in seven trials.[81,85,101,107,118,122,123] Twelve RCTs compared autogenous grafts with CM or ADM.[80,82,86,96,97,100,107,116,117,120,123,124] Two trials evaluated the outcomes of CTG compared to guided bone regeneration (arms that were excluded from the NMA, Table 2 in Supplementary Appendix in online *Journal of Periodontology*) for PSPM.[88,89] Table 1 displays the characteristics of the included studies, their design, interventions, and outcomes.

3.3 | Assessment of the risk of bias

Nine of the included RCTs were considered to have a low risk of bias,[86,88,89,94,97,100,109,118,119] whereas 15[80-83,85,96,101,107,110,116,120,122-124,126] were assigned a moderate risk of bias, and only one was considered to have high risk of bias.[117] Regarding the non-randomized studies, five were assumed of having a low risk of bias,[24,112,113,32,127] six moderate,[41,93,99,105,108,115] and 1 assessed as presenting with a serious risk of bias.[98] Eight case series were classified with having a low risk of bias,[84,90-92,114,34,121,125] whereas seven were assigned to a moderate risk of bias.[87,95,102-104,106,111] Detailed results regarding the assessment of the bias for each selected study can be found in the Supplementary Appendix in online *Journal of Periodontology* (Supplementary Tables 3-5).

Qualitative assessment of studies reporting on peri-implant soft tissue phenotype modification is reported in the Supplementary Appendix in online Journal of Periodontology.

3.4 | Synthesis of results from the network meta-analysis

Due to the reporting of results associated with PSP outcomes, two RCTs were excluded from the NMA.[83,110] Thus,

TABLE 1 Characteristics of the included studies and their interventions

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
Anderson et al. 2014[80]	RCT	Single center, USA, University, sponsored	ADM – bilaminar	Delayed	49, NA, yes	3, 6	6, 6	3.5 ± NA	2.25 ± NA	NA	3.7 ± NA	3.5 ± NA	NA	Both ADM and CTG are effective in increased MT and in reducing concavity dimensions
			CTG – bilaminar	Delayed	49, NA, yes	3, 6	7, 7	3.14 ± NA	2.14 ± NA	NA	3.78 ± NA	3.07 ± NA	NA	
Basegmez et al. 2012[81]	RCT	Single center, Turkey, University, self-supported	FGG – APF	Delayed	59.13, 14/18, no	3, 6, 12	32, 32	0.75 ± 0.36	NA	NA	3.11 ± 0.58	NA	NA	FGG resulted in significantly higher KMW gain than APF
			APF (with no soft tissue grafts)	Delayed	61, 14/18, no	3, 6, 12	32, 32	0.67 ± 0.32	NA	NA	1.83 ± 0.73	NA	NA	
Basegmez et al. 2013[82]	RCT	Single center, Turkey, University, self-supported	ADM – APF	Delayed	51.9, 6/12, no	3, 6	18, 36	0.89 ± 0.31	NA	NA	2.47 ± 0.32	NA	NA	FGG resulted in higher KMW gain than ADM
			FGG – APF	Delayed	58.2, 5/13, no	3, 6	18, 36	1.01 ± 0.34	NA	NA	3.58 ± 0.4	NA	NA	
Bianchi & Sanfilippo 2004[83]	RCT	Single center, Italy, University, NA	CTG – bilaminar	At implant placement	45.4, 58/58, yes	12 – 108	96, 96	NA	NA	NA	NA	NA	NA	Better esthetics and patient satisfaction when CTG was placed at time of implant placement. MBL increased 0.15 mm/year after the first year of loading in the control group, whereas in the CTG group marginal bone level was more stable
			No soft tissue augmentation	NA			20, 20	NA	NA	NA	NA	NA	NA	
Burkhardt et al. 2008[84]	non-RCT	Single center, Switzerland, University, self-supported	CTG – bilaminar	Delayed	NA, 4/6, no	3, 6	10, 10	1.3 ± 1	NA	NA	1.1 ± 0.5	NA	NA	CTG can improve mucosal recession at implant site, however KMW was not increased
Buyukozdemir Askin et al. 2015[85]	RCT	Single center, Turkey, University, self-supported	FGG – APF	Delayed	NA, NA, no	3, 6	20, 20	0.35 ± 0.48	NA	NA	4.4 ± 1.5	NA	NA	FGG provided significant KMW gain and improvement in inflammatory parameters compared to maintenance only. No differences between the groups in terms of MBL
			No soft tissue augmentation (maintenance only)	NA	NA, NA, no	3, 6	20, 20	0.6 ± 0.5	NA	NA	0.6 ± 0.5	NA	NA	

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
			No soft tissue augmentation (control)	NA	NA, NA, no	3, 6	20, 20	3.8 ± 1.23	NA	NA	3.9 ± 1.29	NA	NA	
Cairo et al. 2017[86]	RCT	Single center, Italy, University, sponsored	CM – bilaminar	At second stage	50.3, 10/20, yes	3, 6	30, 30	3.1 ± 1.2	2.1 ± 0.6	NA	4.3 ± 1.2	3 ± 0.7	NA	CTG was more effective than CM in MT gain, whereas similar KMW gain was found between the two groups. Less patient morbidity with CM
			CTG – bilaminar	At second stage	48.3. 6/24, yes	3, 6	30, 30	3.5 ± 1.7	2.1 ± 0.6	NA	4.4 ± 1.5	3.4 ± 0.6	NA	
Covani et al. 2007[87]	non-RCT	Single center, Italy, University, NA	CTG – bilaminar	At implant placement	NA, 5/5, yes	6, 12	10, 10	1.3 ± 0.6	NA	NA	4.1 ± 0.5	NA	NA	Implant placement + CTG showed improved esthetic outcomes and significant KMW gain
D'Elia et al. 2017[88]	RCT	Single center, Italy, University, sponsored	CTG – bilaminar	At implant placement	50.7, 7/8, yes	6, 12	15, 15	3.7 ± 0.8	3.1 ± 1.7	NA	4.86 ± 0.83	3.73 ± 1.13	NA	CTG was found as effective as guided bone regeneration in maintaining facial level when performed in conjunction with implant placement
De Bruyckere et al. 2015[90]	non-RCT	Single center, Belgium, University, sponsored	CTG – bilaminar	Delayed	38, 19/18, no	12	37, 37	NA	1.51 ± 0.46	NA	NA	2.50 ± 0.56	NA	CTG significantly increases MT at implant sites
De Bruyckere et al. 2018[89]	RCT	Single center, Belgium, University, sponsored	CTG -bilaminar	At implant placement	48, 12/9, no	12	21, 21	NA	1.7 ± 0.76	NA	NA	2.68 ± 0.67	NA	No significant differences between CTG and GBR in re-establishing convexity at the buccal aspect of single implants and in terms of providing healthy clinical conditions to the implants
Eghbali et al. 2016[91]	non-RCT	Single center, Belgium, University, sponsored	CTG – bilaminar	Delayed	52, 3/7, no	9	10, 10	NA	1.65 ± 0.41	NA	NA	2.48 ± 0.30	NA	CTG significantly increases MT at implant sites
Eghbali et al. 2018[92]	non-RCT	Single center, Belgium, University, sponsored	CTG – bilaminar	Delayed	38, 19/18, no	12, 60	32, 32	NA	1.52 ± 0.46	NA	NA	2.42 ± 0.63	NA	CTG significantly increases MT at implant sites and provides stable marginal bone level up to 5 year
Fenner et al. 2016[93]	non-RCT	Single center, Switzerland, University, self-supported	CTG – bilaminar	NA	48, NA, yes	86.4	14, 14	NA	NA	NA	NA	NA	NA	Similar results in terms of PD, PI, BOP, KM, mucosal recession and marginal bone level were found in the test and control groups. Stable papillae were observed in sites that received a CTG
			No soft tissue augmentation	NA			12, 12	NA	NA	NA	NA	NA	NA	

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
Fischer et al. 2019[125]	Non-RCT	Multi- center, Germany and Italy, Private practice, self-supported	ADM-bilaminar	At implant placement	50.2, 10/10, yes	6, 24	20, 24	NA	NA	NA	NA	NA	NA	The use of ADM may provide consistent soft tissue augmentation that maintains up to 24-monht follow-up, although graft shrinkage may occur in the first 6 months
Froum et al. 2015[94]	RCT	Single center, USA, University, sponsored	CM – bilaminar	At implant placement	NA, NA, yes	3	17, 17	2.83 ± 1.81	1.06 ± 0.78	NA	3 ± 1.4	1.8 ± 0.6	NA	CM was effective in increasing KMW at implant sites. There was NSSD between CM and control group in terms of MT gain, morbidity and satisfaction outcomes
			No soft tissue augmenta-tion	NA	NA, NA, yes	3	14, 14	2.94 ± 1.3	1.71 ± 0.4	NA	3.8 ± 1.1	1.5 ± 0.4	NA	
Hanser & Khoury 2016[95]	non-RCT	Single center, Germany, Private Practice, self-supported	CTG- bilaminar	At implant placement	37.8, 19/27, no	60	46, 52	NA	NA	NA	NA	NA	NA	Significant MT gain that was maintained up to 5 years together with stable peri-implant parameters
Hosseini et al. 2020[32]	Non-RCT	Denmark, University, self-supported	CTG – bilaminar	At second stage	20, NA, yes	12, 36, 60	10, 10	NA	NA	NA	5.34 ± 1.7	NA	NA	Augmentation using a connective tissue graft may result in better mucosal match and more facial dimension gain compared to sites without soft tissue grafting. NSSD in terms of bone levels
			No soft tissue augmenta-tion		23, NA, yes	12, 36, 60	15, 15	NA	NA	NA	5.43 ± 1.9	NA	NA	
Huber et al. 2018[96]	RCT	Single center, Switzerland, University, sponsored	CTG – bilaminar	NA	43.4, 4/6, yes	6, 12	10, 10	3.2 ± 1.4	2.7 ± 0.4	NA	3.2 ± 0.8	3.1 ± 1.3	NA	CTG and CM showed comparable soft tissue volume up to 1 year
			CM – bilaminar	NA	44.1, 3/7, no	3	10, 10	2.5 ± 0.8	3.2 ± 0.8	NA	2.1 ± 1.2	2.8 ± 0.7	NA	
Hutton et al. 2018[97]	RCT	Single center, USA, University, sponsored	ADM – bilaminar	At implant placement	59.7, 6/4, no	4	10, 10	4.95 ± 1.38	2.4 ± 1.02	NA	4.5 ± 0.94	3.25 ± 1.3	NA	Similar outcomes in terms of KMW and MT gain between ADM and CTG, with ADM showing lower patient morbidity
			CTG – bilaminar	At implant placement	51.2, 5/5, no	4	10, 10	5.3 ± 1.16	2.95 ± 1.17	NA	4.45 ± 1.14	4.15 ± 1.33	NA	
Lee et al. 2010[98]	non-RCT	Single center, Korea, University, self-supported	FGG – APF	At second stage	NA, NA, NA	6	3, 8	0.5	NA	NA	3 ± 1	NA	NA	CM is a viable option to FGG for increasing KMW
			CM – APF	At second stage	NA, NA, NA	6	3, 3	1.3 ± 0.6	NA	NA	3.2 ± 0.8	NA	NA	

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
			APF (with no soft tissue grafts)	At second stage	NA, NA, NA	6	3, 3	3	NA	NA	4.7 ± 0.6	NA	NA	
Linkevicius et al. 2015[99]	non-RCT	Single center, Lithuania, NA, self-supported	ADM – bilaminar	At implant placement	45.3, 31/72, no	12	35, 35	NA	NA	NA	NA	NA	NA	Thin mucosa showed the greatest MBL compared to thick mucosa and thin mucosa augmented with ADM. Increasing STH with ADM significantly reduced the amount of MBL. Naturally thick tissues were able to induce minor bone remodeling
			No soft tissue augmentation (thin mucosa)	NA		12	34, 34	NA	NA	NA	NA	NA	NA	
			No soft tissue augmentation (thick mucosa)	NA		12	34, 34	NA	NA	NA	NA	NA	NA	
Lorenzo et al. 2012[100]	RCT	Single center, Spain, University, supported	CTG – APF	Delayed	63, 3/8, yes	3, 6	11, 11	0.42 ± 0.51	NA	NA	2.75 ± 1.55	NA	NA	CM was as effective as CTG for KMW augmentation
			CM – APF	Delayed	62. 2/8, yes	3, 6	11, 11	0.5 ± 0.52	NA	NA	2.8 ± 0.42	NA	NA	
Oh et al. 2017[101]	RCT	Single center, USA, Private practice, self-supported	FGG – APF	Delayed	65, 4/10, no	6, 12, 18	14, 21	0.5 ± 0.4	NA	NA	3.9 ± 1.9	NA	NA	FGG resulted in significant KMW gain, GI reduction and less crestal bone loss compared to control group
			No soft tissue augmentation	NA	63, 5/9, no	6, 12, 18	14, 20	0.6 ± 0.5	NA	NA	0.4 ± 0.4	NA	NA	
Oh et al. 2020[122]	RCT	Single center, USA, Private practice, self-supported	FGG – APF	Delayed	65.3, 2/9, no	48	11, 18	0.5 ± 0.6	NA	NA	3.6 ± 1.3	NA	NA	The increased KMW following FGG was maintained for 48 months. FGG also showed less mucosal recession than the no-soft tissue augmentation group. Significantly greater marginal bone loss was found for the no-surgery group versus FGG group.
			FGG- APF	Delayed	65, 2/3, no	27	5, 8	0.4 ± 0.5	NA	NA	NA	NA	NA	
			No soft tissue augmentation	NA	66, 3/4, no	48	7, 8	0.7 ± 0.7	NA	NA	0.7 ± 0.7	NA	NA	
Papi et al. 2019[102]	non-RCT	Single center, Italy, University, self-supported	ADM – bilaminar	At implant placement	56.87, 4/6, yes	12	10, 10	1.47 ± 0.23	1.35 ± 0.32	NA	4.17 ± 1.98	4.12 ± 2.12	NA	ADM showed significant KMW and MT gain

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
Papi & Pompa 2018[103]	non-RCT	Single center, Italy, University, self-supported	ADM – bilaminar	At second stage	43.75, 5/7, yes	6, 12	12, 12	1.35 ± 0.32	NA	NA	5.67 ± 2.12	NA	NA	ADM can be successfully used for peri-implant augmentation. Peri-implant health parameter were stable up to 1 year
Park 2006[104]	non-RCT	Single center, Korea, University, self-supported	ADM – APF	Delayed	49.8, 10/0, NA	6	10, 26	0.8 ± 0.6	NA	NA	2.2 ± 0.6	NA	NA	ADM resulted in significant KMW gain and plaque index reduction compared to baseline
Poli et al. 2019[105]	non-RCT	Single center, Korea, University, self-supported	CTG – bilaminar	At implant placement	50.16, 3/3, yes	6, 12	6, 6	NA	1.43 ± 0.41	NA	2.52 ± 0.43	NA	NA	CTG at implant placement and at second stage provides similar MT gain that remained stable up to 1 year
			CTG – bilaminar	At second stage	48.87, 5/3, yes	6, 12	8, 8	NA	1.22 ± 0.27	NA	2.4 ± 0.29	NA	NA	
Puisys & Linkevicius 2015[41]	non-RCT	Single center, Lithuania, NA, NA	ADM – bilaminar	At implant placement	47.3, NA, no	12	32, 32	NA	NA	NA	NA	NA	NA	Significant MBL observed in thin STH. Naturally thick STH and mucosa augmented with ADM showed significant less MBL
			No soft tissue augmentation (thin mucosa)	NA		12	31, 31	NA	NA	NA	NA	NA	NA	
			No soft tissue augmentation (thick mucosa)	NA		12	32, 32	NA	NA	NA	NA	NA	NA	
Puisys et al. 2015[106]	non-RCT	Single center, Lithuania, NA, NA	ADM – bilaminar	At implant placement	42.5, 15/25, no	3	40, 40	NA	NA	1.54 ± 0.51	NA	NA	3.75 ± 0.54	ADM can be successfully used for increase STH
Puzio et al. 2018[107]	RCT	Single center, Poland, University, sponsored	CM – bilaminar	At second stage	42.1, 5/10, yes	3, 12	15, 15	NA	1.21 ± 0.49	NA	NA	2.1 ± 0.5	NA	CTG showed higher MT gain than CM
			CTG – bilaminar	At second stage	41.1, 9/6, yes	3, 12	15, 15	NA	1.15 ± 0.4	NA	NA	2.68 ± 0.96	NA	
			No soft tissue augmentation	NA	43.3, 6/9	3, 12	15,15	NA	1.39 ± 0.7	NA	NA	2.1 ± 0.7	NA	
Puzio et al. 2020[123]	RCT	Single center, Poland, University, sponsored	CM – bilaminar	At second stage	42.1, 5/10, yes	12	15, 15	NA	1.21 ± 0.49	NA	NA	2.1 ± 0.5	NA	Soft tissue augmentation after implantation cause higher bone loss than soft tissue augmentation before implant placement. Lower marginal bone loss was found in presence of thicker gingiva

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
			CTG – bilaminar	At second stage	41.1, 9/6, yes	12	15, 15	NA	1.15 ± 0.4	NA	NA	2.68 ± 0.96	NA	
			No soft tissue augmentation	NA	43.3, 6/9	12	15,15	NA	1.39 ± 0.7	NA	NA	2.1 ± 0.7	NA	
Quiao et al. 2016[108]	non-RCT	Single center, China, University, NA	FGG – APF	1 month after implant placement	41, NA, NA	6	10, NA	NA	NA	NA	3 ± 1.3	NA	NA	FGG showed significantly higher KTW than APF
			FGG – APF	1 month after implant placement	25, NA, NA	6	10, NA	NA	NA	NA	3.5 ± 1	NA	NA	
			APF (with no soft tissue grafts)	NA	44, NA, NA	6	10, NA	NA	NA	NA	1.9 ± 0.3	NA	NA	
Roccuzzo et al. 2016[24]	non-RCT	Single center, Italy, Private Practice, self-supported	FGG – APF	Delayed	52.4, 52/76, yes	120	NA, 11	NA	NA	NA	NA	NA	NA	Implants not surrounded by KM are more prone to plaque accumulation and mucosal recession. FGG can facilitate proper oral hygiene procedure. No differences in terms of MBL, PD and BOP within the groups.
			No soft tissue augmentation (implants with KM)	NA			NA, 63	NA	NA	NA	NA	NA	NA	
			No soft tissue augmentation (implants without KM)	NA			NA, 24	NA	NA	NA	NA	NA	NA	
Rojo et al. 2018[109]	RCT	Single center, Spain, University, self-supported	CTG (from the palate) – bilaminar	At second stage	50.47, 7/9, no	3	16, 18	4.2 ± 1.37	NA	NA	5.07 ± 1.48	NA	NA	CTG (harvested either from the palate or from the tuberosity) is effective in increase soft tissue volume and KMW at implant sites
			CTG (from the tuberosity) – bilaminar	At second stage	54.4, 10/6, no	3	16, 18	3.72 ±1.22	NA	NA	5 ± 1.14	NA	NA	
Sanz et al. 2009[110]	RCT	Single center, Spain, University, sponsored	CM – APF	Delayed	NA	3, 6	NA	NA	NA	NA	NA	NA	NA	Both CTG and CM are effective in increasing KMW, however CM is associated with lower morbidity
		Single center, Spain, University, sponsored	CTG – APF	Delayed	NA	3, 6	NA	NA	NA	NA	NA	NA	NA	

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
Schallhorn et al. 2015[111]	non-RCT	Multicenter, USA, University, sponsored	CM – bilaminar	At second stage	NA, NA, NA	6	30, 35	1.7 ± 1.8	1.5 ± 0.5	NA	2.1 ± 1	2.2 ± 0.9	NA	CM was able to increase KMW and MT
Schmitt et al. 2013[113]	non-RCT	Single center, Germany, University, sponsored	FGG – APF	At second stage	58.5, 6/8, yes	3	7, 24	0.88 ± 0.65	NA	NA	9.81 ± 2.45	NA	NA	FGG and CM showed comparable clinical and histological short-term outcomes
			CM – APF	At second stage		3	7, 25	0.97 ± 0.64	NA	NA	10.32 ± 3.15	NA	NA	
Schmitt et al. 2016[112]	non-RCT	Single center, Germany, University, sponsored	FGG – APF	At second stage	48.5, NA, yes	12, 24, 36, 48, 60	21, 74	0.7 ± 0.69	NA	NA	8.4 ± 2.41	NA	NA	FGG and CM showed comparable clinical and histological long-term outcomes.
			CM – APF	At second stage			27, 102	0.62 ± 0.33	NA	NA	6.15 ± 1.23	NA	NA	
Stefanini et al. 2016[114]	non-RCT	Single center, Italy, University, self-supported	CTG – bilaminar	At implant placement	NA, 8/12, no	12, 36	20, 20	2.25 ± 0.72	1.04 ± 0.16	NA	3.05 ± 0.76	2.73 ± 0.25	NA	CTG was able to provide soft tissue gain in terms of KMW and MT. No signs of peri-mucositis or peri-implantitis were noticed up to 3 years. Stable marginal bone levels were observed
Stimmelmayr et al. 2011[115]	non-RCT	Single center, Germany, NA, NA	FGG – APF	At implant placement	57.7, 13/16, NA	12	10, 24	2.75	NA	NA	3.3	NA	NA	FGG either at implant placement or at second stage resulted in stable KTW around implants up to 1 year
			FGG – APF	At second stage		12	19, 46	3	NA	NA	3.7	NA	NA	
Thoma et al. 2016[116]	RCT	Single center, Switzerland, University, sponsored	CTG – bilaminar	NA	42.7, 4/6, yes	3	10, 10	NA	4.1 ± 2	4.2 ± 1.9	NA	NA[a]	NA[a]	Similar clinical outcomes between CTG and CM in terms of MT and STH
			CM – bilaminar	NA	43.8, 3/7, yes	3	10, 10	NA	2.9 ± 1.5	3.4 ± 1.0	NA	NA[a]	NA[a]	
Thoma et al. 2020[124]	RCT	Single center, Switzerland, University, sponsored	CTG – bilaminar	NA	43.4, NA, yes	6, 12, 36	9, 9	3.2 ± 1.4	2.7 ± 0.4	NA	3.2 ± 1	3.8 ± 1.5	NA	Similar clinical outcomes between CTG and CM, with minimal changes of the peri-implant tissue contour and thickness over time. MBL was stable over time for both groups.
			CM – bilaminar	NA	44.1, NA, no	6, 12, 36	8, 8	2.4 ± 0.8	3.2 ± 0.8	NA	2.5 ± 1.4	3.6 ± 1.5	NA	
Ustaoglu et al. 2020[126]	RCT	Single center, Turkey, University, self-supported	CTG – bilaminar	At implant placement	39.13, 5/10, no	3	15, 15	3.56 ± 1.07	2.16 ± 0.58	2.35 ± 0.58	3.83 ± 0.91	2.82 ± 0.75	2.93 ± 0.64	Both CTG and titanium-prepared platelet-rich fibrin resulted in an increased peri-implant soft tissue thickness. No crestal bone loss was observed in any of the dental implants

(Continues)

TABLE 1 (Continued)

Publication	Study design	No. of centers, Country, Setting, Funding	Treatment	Timing of intervention	Participant age (years), No. Male/Female, Inclusion of smokers	Follow-up time (months)	Patients (n), Implants (n)	Baseline measures (mm ± SD)			Final outcomes (mm ± SD)			Study conclusion
								KMW	MT	STH	KT	MT	STH	
Vellis et al. 2019[117]	RCT	Single center, USA, Private practice, sponsored	CM – APF	Delayed	NA, NA, yes	3, 6	30, 30	1.2 ± 0.7	NA	NA	4.4 ± 1.8	NA	NA	CM achieved comparable results to FGG. The two approaches do not affect probing depth, marginal recession and bleeding on probing.
			FGG – APF	Delayed	NA, NA, yes	3, 6	30, 30	0.9 ± 0.8	NA	NA	4.6 ± 2.2	NA	NA	
Verardi et al. 2019[127]	Non-RCT	Single center, USA and Italy, self-supported	ADM – bilaminar	At implant placement	58.3, 11/13, yes	6	24, 24	NA	NA	1.72 ± 0.38	NA	NA	3.01 ± 0.58	The use of ADM showed superior increase in STH compared to the use of a healing abutment for "tenting effect"
Wiesner et al. 2010[118]	RCT	Single center, Austria, Private practice, NA	CTG	At implant placement	39, 3/7, no	12	10, 10	NA	2 ± 0.47	NA	NA	3.2 ± 0.42	NA	CTG significantly increased soft tissue thickness and esthetics compared to non-augmented sites. No significant differences between the groups in terms of bone loss
			No soft tissue augmentation	NA	39, 3/7, no	12	10, 10	NA	2.05 ± 0.5	NA	NA	1.9 ± 0.32	NA	
Zafiropoulos & John 2016[119]	RCT	Single center, Italy, University, supported	ADM – bilaminar	At implant placement	47.2, 9/5, yes	6	14, 14	NA	1.13 ± 0.4	NA	NA	2.19 ± 0.36	NA	Significantly higher peri-implant MT following ADM
			No soft tissue augmentation	NA	45.1, 9/4, yes	6	13, 13	NA		NA	NA		NA	
Zeltner et al. 2017[120]	RCT	Single center, Switzerland, University, sponsored	CTG – bilaminar	NA	42.7, 4/6, yes	3	10, 10	NA	NA[a]	NA[a]	NA	NA[a]	NA[a]	Similar clinical outcomes between CTG and CM in terms of MT and STH
			CM – bilaminar	NA	43.8, 3/7, yes	3	10, 10	NA	NA[a]	NA[a]	NA	NA[a]	NA[a]	
Zucchelli et al. 2013[121]	non-RCT	Single center, Italy, University, self-supported	CTG – bilaminar	Delayed	NA, 6/14, yes	12	20, 20	1.75	0.9	NA	2	2.45	NA	CTG resulted in a significant increase in KMW and MT
Zucchelli et al. 2018[34]	non-RCT	Single center, Italy, University, self-supported	CTG – bilaminar	Delayed	NA, NA, yes	60	19, 19	1.75	0.9	NA	3	2.6	NA	CTG resulted in a significant increase in KMW and MT at 5 years with respect to 1 year

[a]resulted reported as a change from baseline to follow-up. ADM, acellular dermal matrix; APF, apically positioned flap; BOP, bleeding on probing; CM, collagen matrix; CTG, connective tissue graft; FGG, free gingival graft; GBR, guided bone regeneration; GI, gingival index; KMW, keratinized mucosa width; MBL, marginal bone loss; MT, mucosal thickness; NSSD, not statistically significant difference(s); NA, not available; PD, probing depth; RCT, Randomized controlled trial; STH, supracrestal tissue height

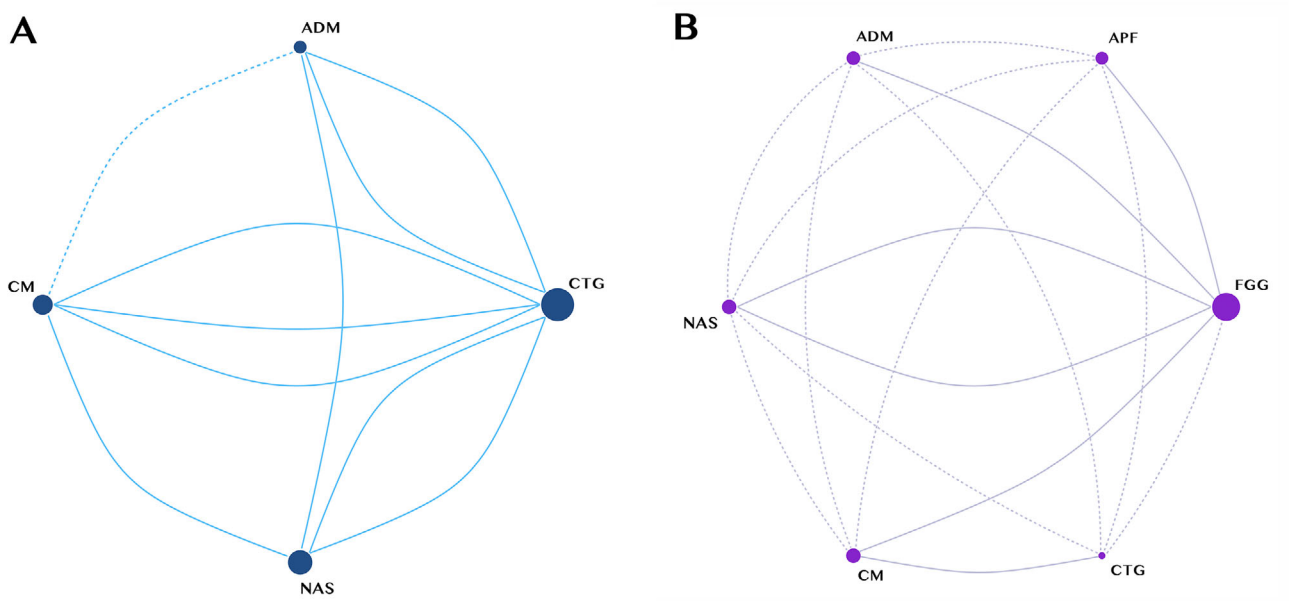

FIGURE 2 Network meta-analysis of eligible comparisons for **A**) bilaminar, and **B**) APF-based approaches. Solid lines connect treatments that are directly compared in at least one study. Interrupted lines show the indirect comparisons for the treatments that have not been previously compared head-to-head in a randomized trial and is formulated through the network model. Studies contributing with only one arm are not presented. Distances are for plot clarity alone and the node size is proportional to the number of treated sites. ADM, acellular dermal Matrix; APF, apically positioned flap; CM, collagen Matrix; CTG, connective tissue graft; FGG, free gingival graft; NAS, non-augmented sites

ultimately 23 RCTs were included in the final quantitative analysis.[80-82,85,86,88,89,94,96,97,100,101,107,109,116-120,122-124,126] Figure 2 displays the generated direct and indirect comparisons for both NMAs, assessing the outcomes of bilaminar (based on 16 RCTs[80,86,88,89,94,96,97,107,109,116,118-120,123,124,126]), and APF-based techniques (based on 7 RCTs[81,82,85,100,101,117,122]).

1) **Network meta-analysis on bilaminar approaches**

Figure 2A displays the results of the pairwise comparisons among the investigated treatment arms from the model for changes in KMW and MT. The variances of the random effect from the model are presented in the Supplementary Appendix in online *Journal of Periodontology* (Supplementary Tables 6 and 7).

3.5 | Keratinized mucosa width as a component of peri-implant phenotype

Among the included arms, none of the treatment groups was able to significantly increase the KMW compared to untreated sites.

When CM was the reference for the comparisons, there were no statistically significant differences between any of the treatment groups in the network model. Similarly, using ADM as the reference, no significant differences were observed among the treatment groups (pairwise comparisons presented in Figure 3).

The timing of soft tissue augmentation (whether at the time of implant placement, at the second stage, or delayed) also did not seem to be significantly related to the obtained results in terms KMW.

Regarding health-related parameters, whereas no significant relationship was observed in the model with PI (0.25 (95% CI [0.249, 0.25], $P = 0.76$)), a negative correlation was observed with PD (-0.33 mm (95% CI [–0.333, –0.332], $P < 0.001$)). Nevertheless, this analysis was only based on the comparison of CTG versus non-intervention control sites because of the limited numbers of studies that reported PD. Furthermore, a comparative analysis on GI could not be performed as only two studies,[85,101] both on the same treatment arm (untreated sites) reported this parameter.

3.6 | Mucosal thickness as an independent parameter of peri-implant phenotype

The network model demonstrated that all the treatment groups significantly increased the MT compared with non-intervention at implant sites, with CTG presenting the highest estimate in the model (1.13 mm (95% CI [0.94, 1.31], $P < 0.001$)), followed by ADM (1.08 mm (95% CI [0.80,

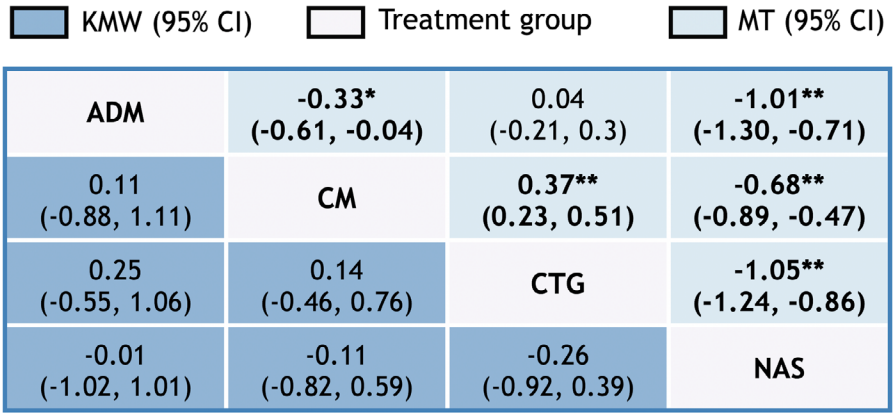

FIGURE 3 Pairwise comparisons from the Network Meta-analysis (NMA) on bilaminar procedures, for changes in KMW and MT. Treatments are reported in alphabetical order. Results are the estimates in millimeter (95% CIs) from the NMA model in the cell in common between the column-defining treatment (defined-treatment 1), and the row-defining treatment (defined-treatment 2). Statistically significant results are in bold. *($P < 0.05$), **($P < 0.001$). CI, Confidence interval; ADM, acellular dermal matrix; CM, collagen matrix; CTG, connective tissue graft; NAS, non-augmented sites

1.35], $P < 0.001$), and CM (0.76 mm (95% CI [0.55, 0.97], $P < 0.001$).

When CM was the reference arm, both treatment groups of CTG (0.36 mm (95% CI [0.23, 0.49], $P < 0.001$)), and ADM (0.31 mm (95% CI [0.04, 0.57], $P = 0.02$)) exhibited significantly higher estimates in terms of MT gain, whereas non-intervention control sites showed significantly less MT (–0.76 (95% CI [–0.97, –0.55], $P < 0.001$)).

Nonetheless, the difference between ADM and CTG did not reach statistical significance. Using ADM as the reference category, the estimate for CTG in the model was 0.048 mm (95% CI [–0.19, 0.28], $P = 0.69$). However, CM (–0.31 mm (95% CI [–0.57, –0.04], $P = 0.02$)), and untreated sites (–1.08 mm (95% CI [–1.35, –0.80], $P < 0.001$)) showed significantly less MT.

Additionally, no significant association was observed with regard to the timing of soft tissue augmentation in relation to that of implant placement; (at the time of second stage (0.17 (95% CI [–0.04, 0.38], $P = 0.16$)), delayed (0.34 (95% CI [–0.03, 0.73], $P = 0.15$)), compared to implant placement).

Regarding health-related parameters, no statistical significance could be observed with regard to changes in PD (0.25 (95% CI [0.17, 0.33], $P = 0.63$)), or PI (–3.17 (95% CI [–8.44, 2.11], $P = 0.52$)). Similar to the previous analysis on KMW, the potential effect on GI could not be investigated because of scarcity of relevant data in the included RCTs.

Last, when the effect of phenotype modification was assessed for its effect on changes on marginal bone loss, based on the articles that had reported these outcomes,[86,89,118,119,123,124] the model showed that compared to control sites, treatment with CTG (–0.10 (95% CI [–0.14, –0.05], $P = 0.02$) on the mesial, and –0.11 (95% CI [–0.17, –0.06], $P = 0.02$) on the distal) and CM (–0.11 (95% CI [–0.17, –0.04], $P = 0.04$) on the mesial, and –0.13 (95% CI [–0.2, –0.05], $P = 0.03$) on the distal) resulted in significantly less marginal bone loss. A correlation that was observed for changes in marginal bone loss on the mesial and distal aspect of the implant sites. Additionally, time itself in this model showed to be a significant predictor for changes in the level of the bone (0.03 (95% CI [0.01, 0.05], $P = 0.01$) and 0.02 (95% CI [0.005, 0.04], $P = 0.03$) for the analysis on mesial and distal, respectively).

2) Network meta-analysis on APF-based approaches

Because of only one study reporting on mucosal thickness,[117] the NMA on APF-based approaches was only conducted on the outcomes of KMW and peri-implant soft tissue dehiscence (Figure 2B). Figure 4 shows the generated pairwise comparison for these two outcomes. For the variances of the included random effects, the reader is referred to the Supplementary Appendix in online Journal of Periodontology (Supplementary table 8).

3.7 | Keratinized mucosa width as a component of peri-implant phenotype

All the included treatment arms, compared with untreated sites showed a significant gain in KMW, in an increasing benefit from APF (2.48 mm (95% CI [1.35, 3.62], $P = 0.04$)), CM (2.96 mm (95% CI [1.82, 4.10], $P = 0.002$)), CTG (2.82 mm (95% CI [1.91, 4.14], $P = 0.007$)), ADM (3.02 mm (95% CI [1.87, 4.17], $P = 0.03$), and FGG (3.67 mm (95% CI [3.03, 4.31], $P = 0.01$); the latter representing the highest estimate in the network model.

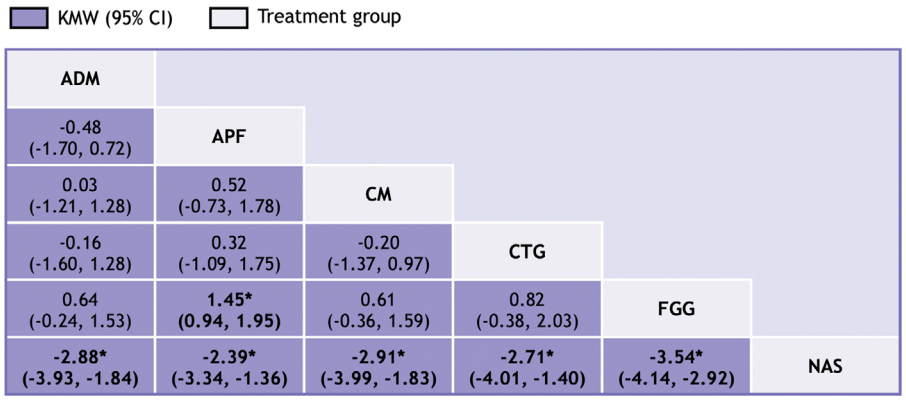

FIGURE 4 Pairwise comparisons from the Network Meta-Analysis (NMA) on non-root coverage procedures, for changes in KMW. Treatments are reported in alphabetical order. Results are the estimates (95% CIs) from the NMA model in the cell in common between the column-defining treatment (defined-treatment 1), and the row-defining treatment (defined-treatment 2). Statistically significant results are in bold. *($P < 0.05$), **($P < 0.001$). CI, confidence interval; ADM, acellular dermal matrix; APF, apically positioned flap; CM, collagen matrix; CTG, connective tissue graft; FGG, free gingival graft; NAS, non-augmented sites

Using APF as the reference, the only significant differences were observed with untreated sites (–2.52 mm (95% CI [–3.48, –1.01], $P = 0.01$)) presenting less, and FGG (1.14 mm (95% CI [0.24, 2.04], $P = 0.02$) displaying greater post-treatment KMW.

An interesting finding was that PD exhibited a negative coefficient of –0.56 mm (95% CI [–1.21, 0.06]) with a *P* value approaching significance (0.08) in the preliminary analysis in the network model with all the treatment arms. However, in a subgroup analysis assessing only treatment of APF plus a graft material (exclusion of APF alone), it was shown that treatment, compared to no intervention, was significantly associated with reduction in PD measures (–0.78 mm (95% CI [–1.38, –0.18], $P = 0.01$). This suggests that KMW augmentation with APF and a graft (regardless of the material) reduces PD.

The model failed to identify a significant association with changes in PI (–0.96 (95% CI [–2.26, 0.33], $P = 0.09$)) with any specific group whereas, the analysis of grafted sites (with APF) versus non-grafted sites showed a significant reduction in PI scores (–1.12 (95% CI [–2.14, –0.11], $P = 0.03$)). Nonetheless, no significant correlations with GI (0.22 (95% CI [–1.77, 2.21], $P = 0.82$)) was observed.

Furthermore, the analysis on peri-implant soft tissue dehiscence revealed a significant reduction with the treatment arms of CM (–0.58 mm (95% CI [–0.86, –0.31], $P = 0.02$)), CTG (–0.45 mm (95% CI [–0.73, –0.17], $P = 0.03$)), and FGG (–0.67 mm (95% CI [–0.85, –0.51]), $P = 0.04$), compared to un-treated sites. It should be noted that, as no data were available for ADM-treated sites, this treatment arm was not assessed in this analysis. Nonetheless due lack of evidence, no analysis could be performed on marginal bone loss.

4 | DISCUSSION

4.1 | Summary of main results

Our results showed a significant increase in KMW when soft tissue grafts, either autogenous or substitutes, were used in combination with APF, whereas no statistically significant KMW gain was obtained following any of the bilaminar techniques. All of the APF treatment groups (FGG, ADM, CTG, CM, and APF) showed superior KMW compared to non-augmented control sites, with FGG displaying the highest estimate in the network model. When APF was the reference, FGG was the only treatment arm that showed a statistically significant gain in KMW. The absence of statistical significance when comparing APF alone with the other graft materials, may be due in part to the limited distributed sample size among other arms, or, possibly, to the fact that CM and ADM do not contain living cells and thus have limited regenerative capability *per se*.[49,128] On the other hand, it was found that KMW did not significantly increase following any of the bilaminar techniques. Although the property of inducing keratinization of the overlying epithelium has been described as a prerogative of CTG in the natural dentition,[49,128] this does not seem to be the case around dental implants when CTG is used as part of a bilaminar approach. The reason for this finding is open to speculation. A possible explanation may be the differing anatomy between the periodontal soft tissue and the peri-implant mucosa, with the latter characterized by a lower number of fibroblasts and reduced vascularity, resembling a scar tissue as opposed to the physiologic environment of a healthy periodontium.[129,130] Last, the changes in KMW, both in the APF and bilaminar

approaches, did not seem to be related to the timing of the soft tissue augmentation procedure (whether at the time of implant placement, during second stage or at a delayed time point). This finding is consistent with a recent systematic review and meta-analysis.[65]

We also observed that soft tissue grafting in combination with APF significantly improved peri-implant KMW, which resulted in reduction of PD, peri-implant soft tissue dehiscence, and PI. Indeed, it has been demonstrated that an adequate band of KMW facilitates patient brushing, even in erratic compliers.[16] Sites exhibiting KMW <2 mm are associated with increased expression of pro-inflammatory mediators, plaque accumulation,[131] marginal bone loss,[17] and severity of peri-implant mucositis.[15] The findings from this review showed that APF + soft tissue grafts reduced PD and peri-implant soft tissue dehiscence. Although unpredictable, it has been observed that mucosal creeping attachment is more likely to occur when autogenous grafts are used.[46,128] Findings from this systematic review suggest that APF in combination with a soft tissue graft can reduce PI and MBL. This is in agreement with the findings reported by Roccuzzo et al. who observed that adequate KMW facilitates proper plaque control.[24] Although other authors did not find an improvement in peri-implant health parameters following KMW augmentation,[24,85,117] Oh et al. compared FGG to oral prophylaxis with no surgical intervention and found significantly lower GI and MBL for implants that had received FGG.[101,122]

Soft tissue augmentation procedures to increase MT are mostly intended to improve esthetic outcomes and/or compensate for volume deficiencies.[9,33,46,49,132] Results from the NMA showed that all bilaminar techniques were effective in increasing MT, with CTG presenting the highest estimate in the model. A recent review using traditional pairwise meta-analysis comparing CTG and CM reported similar findings regarding the superiority of CTG in terms of MT gain.[52] Interestingly, our results also showed superior gain in MT for ADM compared to CM. This finding should be interpreted with caution as this comparison is purely based on the generated indirect comparison from the network model, and, within the limits of our knowledge, ADM and CM have never been directly compared head-to-head in a clinical setting for peri-implant soft tissue augmentation. Nevertheless, higher MT gain with ADM may be because of the nature of the extracellular matrix that purportedly supports cellular migration and revascularization from the surrounding host tissues.[49,133,134] It has been suggested that ADM may mimic the native tissue microenvironment better than xenogeneic CM. Additionally, ADM has superior structural stability and is more resistant to collapse.[49]

Interestingly, MT gain difference between CTG and ADM did not reach statistical significance. Although CTG is considered the gold standard for root coverage purposes,[45,46] MT increase is one of the main expected outcomes of ADM.[49,133,135,136] A comparable gain in gingival thickness between CTG and ADM has also been described.[137] Similarly, Hutton et al. found that ADM and CTG have similar short-term clinical and patient-reported outcomes when used at the time of implant placement to increase MT.[97] Nevertheless, it should be mention that CTG has been generally recommended as the grafting material of choice when treating peri-implant soft tissue dehiscences.[34,35,37,46] Results from the NMA did not reveal an association between MT augmentation and PD or PI reduction, whereas PSPM with bilaminar approach utilizing either CTG or CM showed beneficial effects in marginal bone level changes, such as non-augmented sited displayed a significant higher MBL. This result is in line with previous studies that indicate that soft tissue augmentation may contribute to the stability of marginal bone levels.[83,92,114,123,124] In particular, Puzio et al. found that higher MT was associated with lower MBL.[123] In addition, our results showed that the timing of soft tissue augmentation, whether at implant placement, second stage or delayed, did not affect MT gain.

A network comparison between different soft tissue grafting materials with regard to STH could not be performed. Although Puisys et al. suggested that ADM can be successfully used for increasing STH and reducing MBL,[106] further clinical trials investigating STH augmentation with different grafting materials and their effect on peri-implant health are required. On the other hand, evidence is available pertaining to the influence of initial STH on MBL.[43,68] It has been shown that implants placed in sites presenting thin STH are associated with increased MBL compared to implants placed in the presence of naturally thick STH or STH that was augmented at the time of implant placement.[41,99] Two articles included in this systematic review evaluated the effect of augmenting STH on MBL.[41,99] They concluded that thin mucosa showed the greatest MBL and that STH augmentation using ADM significantly reduced MBL.[41,99] Nevertheless, the 2017 World Workshop has suggested to interpret these conclusions with caution because most of the data emanates from the same research group limiting generalizability of the findings.[58]

4.2 | Agreements and disagreements with other reviews

The 2017 World Workshop stated that there was equivocal evidence regarding the long-term effect of KMW on health and maintenance of dental implants.[58,60] More recently,

proceedings from a consensus workshop[13] based on a systematic review[10] reported that soft tissue grafting at implant sites, compared to non-augmented sites may lead to less PI, GI, and MBL. In order to expand on the existing evidence, we conducted a comprehensive assessment of the evidence pertaining to the comparative efficacy of different interventions aimed at PSPM and their effect on peri-implant health using a network meta-analysis. Based on our knowledge, this is the first analysis comparing the efficacy of different soft tissue grafting procedures aimed at increasing PSPM through the conduction of a NMA. One of the advantages of this approach in the context of this systematic review is the possibility to include heterogeneous treatment arms from trials with different comparative groups,[45] which can aid in compensating for the limited power of traditional meta-analyses that may need to base their conclusions on singular or few articles.[10,52] In line with the review by Thoma et al., we confirmed that APF in combination with FGG is the most effective technique for peri-implant KMW augmentation.[51] In addition, our NMA allowed us to compare different PSPM therapies, also some that were never tested before in a clinical setting.

Qualitative analysis (including both RCTs and non-RCTs) failed to find strong evidence regarding a possible positive effect of APF-based PSPM therapies and MBL, although a previous review concluded that APF + autogenous grafts resulted in significantly bone loss over time compared to control treatments.[10] Nevertheless, the authors stated that their conclusion needs to be interpreted with caution given the limited number of articles included in their meta-analysis and the nature of the studies (mostly non-RCTs).[10] Interestingly, we observed that PSPM with bilaminar approach utilizing either CTG or CM showed beneficial effects in marginal bone level changes, such as non-augmented sited displayed a significant higher MBL. This is in line with the previously mentioned review.[10] In addition, in accordance with a recent review from Cairo et al., we confirmed that the CTG achieved higher MT gain than CM.[83] However, we also found that ADM is as equally effective as CTG (and superior than CM and non-grated sites) in terms of MT gain.

Lastly, it has to be mentioned that although a thorough search strategy was employed, it may still be possible that some relevant literature was not identified in the search process of the present study. As such, the findings from this review can serve as a recommendation for future investigations to be more comprehensive on the above parameters, including patient-reported outcomes.

Quality of evidence and limitations of the current article are discussed in the Supplementary Appendix available in online Journal of Periodontology.

5 | CONCLUSIONS

The following conclusions can be drawn on the basis of the findings from this study:

1) APF in combination with FGG is the most effective technique for peri-implant KMW augmentation. Contrastingly, bilaminar approaches were not associated with a significant gain in KMW, regardless of the soft tissue grafting material employed.
2) Bilaminar techniques in combination with CTG or ADM were superior to CM in terms of MT gain. PSPM via a bilaminar approach utilizing either CTG or CM showed beneficial effects on marginal bone level stability.
3) KMW augmentation via APF in combination with a soft tissue grafting material is associated with significant reductions in probing depth, peri-implant soft tissue dehiscence, and plaque index.
4) STH augmentation at the time of implant placement may contribute to marginal bone level stability.
5) Future studies are warranted to evaluate the effect of PSPM on peri-implant health in the long-term, in particular regarding the effect on MBL stability and patient-reported outcome measures.

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AUTHOR CONTRIBUTION

L. Tavelli: Design of the study, acquisition and interpretation of data, manuscript preparation, and the initial draft, final reviewal of the work; accountable for all aspects of the work. **S. Barootchi**: Conception and design of the study; analysis, and interpretation of data; Initial and final drafting of the work; final approval of the version to be published; accountable for all aspects of the work. **G. Avila-Ortiz**: Data acquisition and examination; contribution to manuscript writing, critical review of the final draft, accountable for all aspects of the work. **I. Urban**: Study design; data interpretation; final approval of the version to be published and critical reviewal of the manuscript draft, and accountable for all aspects of the work. **W. Giannobile**: Final approval of the version to be published, contribution to the writing and critical reviewal of the drafted manuscript, and accountable for all aspects of the work. **H-L Wang**: Design of the study; critical review of

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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