Stability of biomaterials used in adjunct to coronally advanced flap: A systematic review and network meta-analysis

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Abstract
Aim: The objective of this network meta-analysis was to rank different biomaterials used in adjunct to coronally advanced flap (CAF), based on their performance in root coverage for Miller’s Class I and II gingival recessions.

Materials and methods: An electronic database search was carried out in PUBMED, CENTRAL, SCOPUS, and EMBASE to identify the eligible articles and compiled into the citation manager to remove the duplicates. The primary outcome was keratinized gingival tissue width (KGW) and percentage of root coverage (%RC). The treatment effect of different biomaterials was estimated using predictive interval plots and ranked based on biomaterials performance, using multidimensional scale ranking.

Results: CAF + connective tissue graft (CTG), CAF + platelet concentrate matrix (PCM) and acellular dermal matrix (ADM) ranked at the top positions in performance in improving KGW. The highest ranked materials in improving percentage of root coverage in gingival recession were CAF + collagen matrix (CM) + gingival fibroblasts (GF), CAF + ADM + platelet rich plasma (PRP) and CAF + ADM, as compared to CAF alone.

Conclusion: CTG, ADM, platelet concentrates, and CM + GFs, when used in adjunct to CAF, showed improved stability over ≥12 months of follow-up, better percentage of root coverage, and improved keratinized gingival width.

KEYWORDS
CAF, clinical attachment level, keratinised tissue width, network meta-analysis, oral, recession height, recession width, regeneration, root coverage, soft tissue, systematic review

1 INTRODUCTION

Gingival recession (GR) is characterized by displacement of the gingival margin below the level of cemento-enamel junction (Cortellini & Bissada, 2018). Several etiological factors like age, anatomical, physiological, pathological, trauma, hygiene, abnormal frenum attachment, and so on, were identified for this condition (Fu et al., 2012) which may account for its relatively high incidence in the population (Rios et al., 2014; Susin et al., 2004). It affects more than 50% of population including healthy individuals. Recession of 1 mm or more is prevalent in aged 30 years and older. The risk increases with age. Root exposure leads to hypersensitivity, cervical caries, aesthetics complications, and non-carious cervical lesions (Jepsen et al., 2017).

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Root coverage procedures (RCP) have shown to be effective in treating single and multiple GRs (Cairo et al., 2014; Tavelli, Baroouchi, et al., 2018; Tavelli, Baroouchi, et al., 2019; Tavelli, Ravidà, et al., 2019), and in literature, several techniques were proposed. Nevertheless, the superiority of coronally advanced flap (CAF) combined with connective tissue graft (CTG) is clear. Indeed, CAF + CTG is a gold standard in RCP for the best outcomes achieved in terms of mean root coverage, keratinized tissue width, gingival thickness and aesthetics results (Zucchelli et al., 2020).

However, the presence of a second surgical site, patient morbidity, and limited availability are the main drawbacks that have been largely described for CTG (Tavelli, Asa‘ad, et al., 2018; Tavelli, Baroouchi, et al., 2019; Tavelli, Ravidà, et al., 2019). For this reason, several CTG substitutes were introduced including Platelet rich plasma (PRP) or Platelet rich fibrin (PRF), acellular dermal matrix (ADM), enamel matrix derivative (EMD), and xenogeneic collagen matrix (CMX). These biomaterials suffer from limitations in term of shape, consistency and size. PRF is a living cellular graft enriched with growth factors and it is a good alternative to CAF for the availability and the easy handling (Doohan et al., 2006; Miron et al., 2020). The ADM is soft CTG generated by a de-cellularization process preserving the extracellular skin matrix with high costs and it is not in use for ethical problems in diverse countries (McGuire et al., 2020; Tavelli et al., 2020). EMD is a porcine fetal tooth material extracted and manipulated as a gel used as an enhancer in oral regenerative procedures (McGuire & Nunn, 2003). CMX is another biomaterial, which has different layers of collagen fibers and porous layer facilitating blood clot formation and in-growth of tissue from adjacent sites (McGuire & Scheyer, 2016; Vignoletti et al., 2011).

Several studies revealed the comparison among CAF + CTG and each alternative therapy during a follow-up period of 6–12 months showing divergent results (Keceli et al., 2015; McGuire & Scheyer, 2010; Tonelli et al., 2018). According to the authors in the literature, a direct, indirect and mixed evidence for all these biomaterials contributing to the success of root coverage is not present and data extracted from non-systematic comparisons might be confusing and not well interpreted. In addition, the data from all studies are heterogeneous (differences in estimates of effect across studies that assessed the same comparison), which makes difficult to compare all materials. A conventional pairwise meta-analysis results in only one pooled effect estimate. Therefore, a novel method of weighing the effect estimate through network meta-analysis (NMA) has been proposed.

Previous network systematic reviews tried to collect data evaluating the clinical advantages for each CTG substitute with several limitations such as the follow-up period of 6-months which might be a limit, the inclusion of randomized clinical trials (RCTs) with a high risk of bias influencing results and the inclusion of RCTs with smoker patients or RCTs where the absence or presence of smoker patients was not reported (Buti et al., 2013; Moraschini et al., 2020). Thus, the purpose of this systematic review and NMA was to compare the clinical effects among patients who have one or more gingival recession sites and corrected with intervention of CTG substitutes and compared with controls or CAF alone or in combination for regeneration of keratinized gingival width (KGW), clinical attachment level (CAL), recession width (RW), recession height (RH), pocket depth outcomes during a long follow-up period.

2 MATERIAL AND METHODS

This review was performed in accordance with of PRISMA guidelines. The protocol for this review and NMA was registered in PROSPERO with registration ID: CRD42020208010.

The eligibility of study was decided based on PICO format.

Type of Patients: Patients who had one or more than one site of gingival recession was considered for assessment and further review analysis.

Type of Intervention: CAF or/and CTG Substitutes.

Type of Comparator: Compared with Placebo, Control or CAF or/and combination of CAF + biomaterials or CTG substitutes.

Type of outcomes: KGW, CAL, Recession Height, Recession Width, Pocket Depth were the outcomes.

Type of Duration: More than 6 months’ follow-up periods.

2.1 Research question

What is the treatment effect of different biomaterials like CTG, EMD, ADM, PRP/PRF, CMX, and combination of these when used in adjunct to CAF for root coverage?

2.2 Search strategy

An electronic database search was carried out in PUBMED, CENTRAL, SCOPUS, and EMBASE to identify the potentially eligible articles using the following strategy:

“((((Coronally advanced flap) OR (CAF)) OR (modified coronally advanced flap)) OR (coronally displaced flap)) AND (((((((((Enamel matrix derivative) OR (Connective tissue graft)) OR (Guided tissue regeneration)) OR (Collagen matrix)) OR (Acellular dermal matrix)) OR (platelet rich fibrin) OR (platelet rich plasma)) OR (PRF)) OR (PRP)) OR (barrier membrane)) OR (amniotic membrane)) OR (hyaluronic acid)) OR (Emodogain)) OR (CTG))”.

A manual search in periodontal journals like Journal of Clinical Periodontology, Journal of Periodontal Research, Journal of Periodontal and Implant Science, International Journal of Periodontics and Restorative Dentistry, and Journal of Periodontology. There were no limits or filters applied during the search. Both studies relevant to the topic in areas of systematic reviews and clinical trials were searched.

2.3 Inclusion criteria

1. Randomized Clinical Trials (Both parallel and split mouth design)
2. Study follow up duration at least 12 months
3. Minimum sample size of 10 per group
4. CAF procedure should be employed both in test and control group.
5. The test group should have any of the biomaterials in adjunct to CAF compared to control group with a different biomaterial or none in adjunct to CAF.
6. Treatment of Class 1 and 2 gingival recessions only.
7. Both isolated and multiple recession

2.4 | Exclusion criteria

1. Studies not in English
2. Study participants under any medication which could influence the outcome of treatment.
3. Teeth with non-carious cervical lesions (NCCL)
4. Animal studies

2.5 | Study selection

The studies from the databases searches were compiled into citation manager to remove duplicates and screened for all titles and abstract by two independent reviewers (M.K and A.C.D). The eligible studies were then subjected to full text assessment and included for qualitative assessment. In case of disagreement or uncertainty while selecting the eligible articles, an expert third reviewer (M.D.F) was consulted until a consensus was reached. Detailed reasons were mentioned for all excluded studies.

2.6 | Data extraction

The qualitative data was extracted using excel spreadsheet. The data extraction was carried out by using two independent reviewers (M. Dd, H.A.V.). In cases like missing or unclear data or need for additional data or raw data, the authors were approached through emails or telephone for enquiring the details of missing or unclear information.

2.7 | Outcomes

The primary outcomes that were assessed in this review were keratinized gingival width (KGW) and the percentage of root coverage (%RC). The secondary outcomes assessed included CAL, RW, and RD.

2.8 | Data synthesis

The data extracted were both qualitative and quantitative. The former were related to demographics of the study and type of publication. The quantitative data for the different outcomes allowed to undertake NMA. The NMA enables to develop a network geometry plot, where the number of studies and subjects between the comparators are projected. The risk of bias in each network was also estimated. The predictive interval plots (PI) were calculated to predict the effects of future clinical studies incorporating heterogeneity. The surface under the cumulative ranking curve (SUCRA) was calculated for each treatment. Treatments were ranked based on their respective performances. Treatments with SUCRA values with higher percentage of being first were ranked higher and values with lower percentage were ranked lower (0–100%). The multidimensional scale ranking was employed to rank the biomaterials based on their dissimilarity. The network estimates for all comparisons are

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**FIGURE 1** PRISMA flow chart diagram
treated as proximity data aimed to reveal their latent structure. By this, the dissimilarity between any two treatments was distinguished. NMA was carried out using Stata version 16 (StataCorp, College Station, TX) by a single reviewer (S.K).

3 | RESULTS

This qualitative and NMA analysis was carried out by assessing 39 RCTs analyzing the stability of CAF when used alone or in combination with different biomaterials in treatment of class I and II gingival recession defects, over at least 12 months follow-up. The electronic database search and manual search of related journals and bibliographies yielded a total of 1223 articles. The searches from different databases were imported to a citation manager (ENDNOTE) to identify 938 articles after removing duplicates. All the articles were subjected to title and abstract screening, and were narrowed down to identify 56 potentially eligible studies. These studies were subjected to detailed full text assessment by two independent reviewers. Out of 56 eligible studies, 39 RCTs were included in this systematic review and 19 were considered for NMA. The detailed process of study selection is provided in the PRISMA flow chart (Figure 1). The rest of 17 articles were excluded with detailed reason for exclusion (refer Table 1).

3.1 | Characteristics of included studies

The demographic and interventional characteristics of all included studies are presented in Tables 2 and 3, respectively.

This systematic review analyzed a total of 1733 sites from 936 participants included in 39 RCTs. The trials included 546 females and 390 male participants and the age range of the participants recruited in the included RCTs were 18–74 years.

3.2 | Network meta-analysis

For the NMA, 19 RCTs with a total of 858 teeth in in the entire network was considered.

3.2.1 | Keratinized gingival width

The most common comparator is between CAF, CAF + CMX, CAF + CTG and CAF + EMD. The risk of bias is found to be low between CAF and CAF + CM and high between other comparisons (Figures 2–5). A total of N = 858 patients are included in the entire network. There are three studies included in CAF and CAF + CTG and four studies in CAF and CAF + EMD. The percentage contribution of each direct comparison in the entire network CAF and CAF + CTG (13.33%) followed by CAF and CAF + rhPDGF-BB + TCP (10.33%) and that of each pairwise summary effect is from CAF and CAF + ADM (100%) followed by CAF and CAF + CTG (99.0%). CAF + GTR(NonBio) (11) and CAF + CMX (12) have significant variance and inconsistency. CAF + GTR-Bio and CAF + GTR-NonBio more likely to perform poor in future studies in gaining width thickness of gingival recession cases. A favorable outcome is expected through CAF + PCM and CAF + CTG in present (Crl) and future studies (Prf). CAF + CTG and CAF + PCM are ranked higher in SUCRA ranking. GTR Bio and Non-Bio most distinct and dissimilar among other materials as illustrated in MDS rank.

3.2.2 | Percentage of root coverage

The network geometry plot illustrates the total number of subjects (N = 826) and comparisons between each intervention (Figures 6–9). The number of RCT in CAF and CTG are two and CAF + PCM and CAF + CTG (99.04) followed by CAF + ADM and CAF + CMX (98.36). The Majority of indirect evidence contribution is

| TABLE 1 | List of excluded studies |
|---|---|
| **SL no.** | **Study** | **Reason of exclusion** |
| 1. | Tavelli, Barootchi, et al. (2019); Tavelli, Ravida, et al. (2019) | Coronally advanced flap compared to tunnel technique |
| 2. | Stefanini et al. (2018) | Not a randomized clinical trial but a case series |
| 3. | Bellver-Fernández et al. (2016) | Test group has less than 10 sites |
| 4. | Wang et al. (2015) | Same biomaterial used in both groups |
| 5. | Wang et al. (2014) | Same biomaterial used in both groups |
| 6. | Zucchelli et al. (2014) | Same biomaterial used in both groups |
| 7. | Aroca et al. (2013) | Tunnel technique has been used in both the groups |
| 8. | McGuire et al. (2012) | Less than 10 patients as sample size |
| 9. | Aleksic et al. (2010) | Study in Russian language |
| 10. | Aroca et al. (2009) | Follow up till 6 months |
| 11. | Pourabbas et al. (2009) | Follow up till 6 months |
| 12. | Moses et al. (2006) | Two separate procedures have been compared |
| 13. | Dominiak et al. (2006) | Three separate procedures have been compared |
| 14. | Nemcovsky et al. (2004) | Inclusion of cervically abraded teeth |
| 15. | Wennström et al. (1996) | Non-randomized, prospective clinical study |
| 16. | Pini-Prato et al. (2010) | Non randomized study |
| 17. | Henriques et al. (2010) | Class III gingival recessions |
### TABLE 2  Demographic characteristics of included studies

| Sl no. | Author and year | Study design | Age in years (range, mean SD) | Type of recession | No. of patients | No. of sites | Test procedure | Control procedure | Follow-up |
|--------|-----------------|--------------|-------------------------------|-------------------|----------------|-------------|---------------|------------------|-----------|
| 1.     | Barakat and Dayoub (2020) | RCT split-mouth | 20–45 | Single | 20 | 40 | CAF + PCM | CAF + CTG | 12 months |
| 2.     | Rotundo et al. (2021) | RCT parallel | > 18 | Multiple | 24 | 61 | CAF + CMX | CAF | 12 months |
| 3.     | Aydinyyurt et al. (2019) | RCT split-mouth | 18–55 | Single | 19 | 38 | CAF + CTG = EMD | CAF + CTG | 12 months |
| 4.     | Pilloni et al. (2019) | RCT parallel | 21–47 | Single | 30 | 30 | CAF + HA | CAF | 18 months |
| 5.     | Rotundo et al. (2019) | RCT parallel | > 18 | Multiple | 24 | 61 | CAF + CMX | CAF | 12 months |
| 6.     | França-Grohmann et al. (2019) | RCT split-mouth | 29.74 | Single | 30 | 30 | CAF + EMD | CAF | 12 months |
| 7.     | Gürlek et al. (2020) | RCT split-mouth | > 18 | Multiple | 15 | 82 | CAF + ADM | CAF + CTG | 18 months |
| 8.     | Matoh et al. (2019) | RCT parallel | > 18 | Multiple | 24 | 61 | CAF + CMX | CAF | 12 months |
| 9.     | Alexandre et al. (2018) | RCT split-mouth | 37–63 | Single | 25 | 25 | CAF + CTG | CAF | 108 months |
| 10.    | Kuka et al. (2018) | RCT parallel | 21–41 | Multiple | 24 | 52 | CAF + PRF | CAF | 12 months |
| 11.    | Rasperini et al. (2018) | RCT parallel | > 18 | Single | 20 | NR | CAF + CTG | CAF | 60 months |
| 12.    | Cristini et al. (2018) | RCT split-mouth | 20–67 | Multiple | 12 | 84 | CAF + ADM + PRP | CAF + ADM | 12 months |
| 13.    | Abou-Arraj et al. (2017) | RCT parallel | 24–74 | Single | 17 | 17 | CAF + ADM-A | CAF + ADM-B | 12 months |
| 14.    | Jepsen et al. (2017) | RCT split-mouth | 20–73 | Single | 18 | 36 | CAF + CMX | CAF | 36 months |
| 15.    | Cairo et al. (2016) | RCT split-mouth | 20–53 | Multiple | 32 | 74 | CAF + CTG | CAF | 12 months |
| 16.    | McGuire & Scheurer, (2016) | RCT split-mouth | 51.3 ± 13.9 | Single | 17 | 34 | CAF + CMX | CAF + CTG | 60 months |
| 17.    | Godarthi et al. (2016) | RCT split-mouth | 41.4 ± 7.6 | Single | 14 | 28 | CAF + PPG | CAF + ADM | 12 months |
| 18.    | Stefanini et al. (2016) | RCT split-mouth | 39.5 ± 13.8 | Multiple | 45 | 41 | CAF + CMX | CAF | 12 months |
| 19.    | Lops et al. (2015) | RCT parallel | 46 | Single | 28 | 28 | CAF + CTG | CAF | 12 months |
| 20.    | Cairo et al. (2015) | RCT split-mouth | 20–53 | Multiple | 32 | 74 | CAF + CTG | CAF | 12 months |
| 21.    | McGuire & Scheurer, (2016) | RCT split-mouth | 51.3 ± 13.9 | Single | 17 | 34 | CAF + CMX | CAF + CTG | 60 months |
| 22.    | Cairo et al. (2015) | RCT split-mouth | 20–53 | Multiple | 32 | 74 | CAF + CTG | CAF | 12 months |
| 23.    | Ahmedbeyli et al. (2014) | RCT parallel | 22–40 | Multiple | 24 | 48 | CAF + ADM | CAF | 12 months |
| 24.    | Zucchelli et al. (2014) | RCT parallel | >18 | Multiple | 50 | 50 | CAF + CTG | CAF | 60 months |
| 25.    | Cardaropoli et al. (2014) | RCT parallel | 38.4 ± 11.1 | Multiple | 32 | 113 | mCAF + CM | mCAF | 12 months |
| 26.    | Alkan and Parlar (2013) | RCT split-mouth | 35–53 | Multiple | 12 | 56 | CAF + EMD | CAF + CTG | 12 months |
| 27.    | Kuis et al. (2013) | RCT split-mouth | 20–53 | Multiple | 37 | 114 | CAF + CTG | CAF | 60 months |
| 28.    | Köseoğlu et al. (2013) | RCT split-mouth | 19–41 | Single | 11 | 22 | CAF + CMX = GF | CAF + CMX | 12 months |
| 29.    | Roman et al. (2013) | RCT split-mouth | 21–28 | Both | 42 | 57 | CAF + CTG = EMD | CAF + CTG | 12 months |
| 30.    | Kumar and Murthy (2013) | RCT split-mouth | 18–60 | Single | 12 | 24 | CAF + PCG | CAF + CTG | 12 months |
| 31.    | Cordaro et al. (2012) | RCT split-mouth | 18–60 | Multiple | 10 | 58 | CAF + EMD | CAF | 24 months |
| 32.    | Cardaropoli et al. (2012) | RCT split-mouth | 21–59 | Multiple | 18 | 22 | CAF + CMX | CAF + CTG | 12 months |
| 33.    | Alkan and Parlar (2011) | RCT split-mouth | 23–42 | Single | 12 | 24 | CAF + EMD | CAF + CTG | 12 months |
| 34.    | Jankovic et al. (2010) | RCT split-mouth | 21–48 | Single | 20 | 40 | CAF + EMD | CAF + PRF | 12 months |
| 35.    | Del Pizzo et al. (2005) | RCT split-mouth | 18–56 | Single | 15 | 30 | CAF + EMD | CAF | 24 months |

(Continues)
from CAF and CAF + CTG (41.15%) followed by CAF + CTG and CAF + PRF (20.54%). The evidence from entire network contribution is between CAF and CAF + ADM (9.87%) and CAF and CAF + CMX (8.34%).

There is no statistically significant inconsistency in the loop formed by CAF (01), CAF + PCM (03) and CAF + CMX (08) as the lower limit confidence intervals reaches the zero line. CAF + rhPDGF-BB + TCP and CAF + CTG + EMD more likely to perform poor in future studies. It is predicted that CAF + CM + GF treatment would be 73.86% successful followed by CAF + ADM + PRP (45.83%).

CAF + CM + GF and CAF + ADM + PRP ranked higher in SUCRA ranking. Multidimensional scale (MDS) ranking shows that CAF + CTG and CAF + ADM + PRP are the most distinct interventions in improving the outcomes of root coverage in gingival recessions.

### 3.2.3 Clinical attachment level

The highest ranked materials for this specific outcome in CAL were CAF + ADM and CAF + PRF in gingival tissue reconstruction. The effect estimate for CAF + ADM was 1.79(1.21, 2.84) and CAF + PRF was 1.43(0.99, 2.08) (Supplementary Figures 1(a)–(d)).

### 3.2.4 Recession width

The highest ranked materials for RW gain in gingival recession were CAF + CTG and CAF + ADM. The effect estimate was 0.75(0.40, 1.39) and 0.37(0.11, 1.23) for CAF + CTG and CAF + ADM, respectively (Supplementary Figures 2(a)–(d)).

### 3.2.5 Recession height

The highest ranked materials for RD gain were CAF + ADM and CAF + PCM. The effect estimate was found to be 2.03(1.38, 3.00) for CAF + ADM and 1.61 (1.04, 2.49) for CAF + PCM (Supplementary Figures 3(a)–(d)).

### 3.3 GRADE analysis

The overall level of evidence for the regenerative material is moderate. We predominantly downgraded the rating of the evidence due to different levels of risk of bias and imprecision (Table 4).

### 4 DISCUSSION

Our results from NMA explored the effectiveness of different biomaterials in periodontal regeneration (i.e., Gingival Recession). KGW and percentage of root coverage are considered as primary outcomes for validating the successful periodontal regeneration by a biomaterial (Lang & Löe, 1972). We found that, CAF + CTG ranked with highest probability followed by CAF + PCM in keratinised tissue width regeneration (Figure 5). A favorable outcome is expected through CAF + PCM and CAF + CTG as indicated from effect sizes, CrI and PrI. Similarly, CAF + CTG ranked with highest probability followed by CAF + ADM + PRP in favorable outcomes in percentage of root coverage. It is predicted that, CAF + CM + GF treatment would be 73.86% more successful followed by CAF + ADM + PRP (45.83%) (Figure 9).

The ROB among studies that included CAF and CAF + CMX intervention was high and ROB between CAF and CAF + CM was low. Other studies were unclear or had moderate ROB in keratinised gingival width (KGW) outcome (Figure 1a). Similarly, ROB was high among majority of the comparisons except the comparison between CAF Vs CAF + CM for percentage of root coverage (Figure 2). The ROB for all the included studies was illustrated in Figure 10. According to the inconsistency plot, the loop formed by CAF, CAF + CTG, CAF + EMD, CAF + GTR (Nonbio) and CAF + CM had significant inconsistency in KGW outcome (Figure 1b). Similarly, CAF, CAF + PCM, CAF + CM, CAF + CTG + EMD and CAF + EMD had significant inconsistency in percentage of root coverage outcome (Figure 3). The overall evidence from all the comparisons for KGW and percentage of root coverage was found to be moderate (Table 3). The ranking of materials rated highest and lowest should be interpreted carefully by taking ROB and inconsistencies factors between these comparisons and dissimilarity between the materials illustrated by multidimensional scaling (Figure 1(e) and 5(b)).
| Author and year            | Procedure | Test biomaterial | Type of biomaterial | Trade name - test | Control biomaterial | Type of biomaterial | Trade name - control | Surgery time (test) | Surgery time (control) | Outcomes assessed       |
|---------------------------|-----------|------------------|---------------------|-------------------|---------------------|---------------------|---------------------|----------------------|------------------------|------------------------|
| Bankskat and Dayoub (2020)| CAF       | CMX              | XENO                | Mucograft collagen matrix; Geistlich Pharma | CTG                | AUTO                | Autologous          | NR                   | NR                     | RD, PD, CAL, WKG, RC%, CRC%, aesthetic score (RES) and pain intensity |
| Rotundo et al. (2021)     | CAF       | CMX              | XENO                | Geistlich Mucograft®, Geistlich Pharma AG | None               | -                   | None                | NR                   | NR                     | PL, FMB, RD, WKG, GT, PD |
| Aydinoyr et al. (2019)    | CAF       | EMD              | XENO                | Emdogain®; Straumann, Basel, Switzerland    | CTG                | AUTO                | Autologous          | NR                   | NR                     | RD, RW, RC%, CRC%, aesthetic score (RES) |
| Pilloni et al. (2019)     | CAF       | HA               | ALLP               | HydDENT BG, Bioscience, Germany             | None               | -                   | None                | NR                   | NR                     | RD, CAL, PD, WKG, CRC%, RC%, pain intensity |
| Rotundo et al. (2019)     | CAF       | CMX              | XENO                | Geistlich Mucograft®, Geistlich Pharma AG  | None               | -                   | None                | 47.3 ± 5.8           | 36.1 ± 4.6              | RD, RW, BOP, PI, PD, CAL, WKG, GT |
| França-Grohmann et al. (2019) | CAF       | semilunar       | EMD                | Emdogain®; Institut Straumann AG, Basel, Switzerland | None               | -                   | None                | NR                   | NR                     | RD, RW, WKG, GT, PD, CAL |
| Gülfek et al. (2020)      | Modified CAF | ADM         | ALLO               | Mucoderm, Botiss GmbH, Berlin, Germany       | CTG                | AUTO                | Autologous          | NR                   | NR                     | RD, RW, WKG, PD, CAL |
| Match et al. (2019)       | CAF       | CM               | XENO                | Osseobiol Dema, Tecnooss                     | CTG                | AUTO                | Autologous          | NR                   | NR                     | RD, PD, CAL, WKG, GT, RC% |
| Franceti et al. (2018)    | CAF       | CTG              | AUTO               | Autologous                                    | None               | -                   | None                | NR                   | NR                     | RD, CRC%, WKG, WL, RC% |
| Kuka et al. (2018)        | CAF       | PRF              | BIO                | Autologous                                     | None               | -                   | None                | NR                   | NR                     | RD, RW, PD, CAL, GT, WKG, PI, GL and BOP |
| Rasperini et al. (2018)   | CAF       | CTG              | AUTO               | Autologous                                     | None               | -                   | None                | NR                   | NR                     | RD, PD, CAL, WKG, CRC% |
| Çetiner et al. (2018)      | CAF       | PRP              | BIO                | Curasan, Pharma Gmbh AG, Lindigstrab, Germany | ADM                | ALLO                | SureDerm, Seoul, Korea | NR                   | NR                     | RD, RW, WKG, PI, GL, PD, CAL, RC% |
| Abou-Anaj et al. (2017)   | CAF       | ADM-A            | ALLO               | AlloDerm BioHorizons                            | ADM-B              | ALLO                | Puros Dermis Zimmer Biomet | NR                   | NR                     | WKG, RD, GT |
| Jepsen et al. (2017)      | CAF       | CMX              | XENO                | NR                                              | None               | -                   | None                | NR                   | NR                     | RD, CRC%, RD, WKG, GT, CAL, PD |
| Cairo et al. (2016)       | CAF       | CTG              | AUTO               | Autologous                                     | None               | -                   | None                | NR                   | NR                     | RD, CRC%, PD, CAL, WKG, GT |
| McGuire and Scheyer (2016) | CAF       | CMX              | XENO                | NR                                              | CTG                | AUTO                | Autologous          | None                | NR                     | RD, CRC%, WKG, PD and CAL |
| Godavarthi et al. (2016)  | CAF       | PPG              | BIO                | Autologous                                     | ADM                | ALLO                | AlloDerm BioHorizons | NR                   | NR                     | RD, CRC%, WKG, PD, CAL |
| Stefanini et al. (2016)   | CAF       | CMX              | XENO                | Geistlich Mucograft®, Geistlich Pharma AG     | None               | -                   | None                | NR                   | NR                     | RD, RW, WKG, GT, CAL, PD |
| Lops et al. (2015)        | CAF       | CTG              | AUTO               | Autologous                                     | None               | -                   | None                | NR                   | NR                     | RD, WKG, PD, CAL |
| Cairo et al. (2015)       | CAF       | CTG              | AUTO               | Autologous                                     | None               | -                   | None                | NR                   | NR                     | RD, WKG, PD, CAL |
| Milinkovic et al. (2015)  | CAF       | AFC               | AUTO               | Autologous                                     | CTG                | AUTO                | Autologous          | NR                   | NR                     | RD, WKG, CAL |
| McGuire et al. (2014)     | CAF       | rhPDGF-BB        | BIO                | GEM21-S                                         | CTG                | AUTO                | Autologous          | NR                   | NR                     | RD, CAL, PD, WKG, RC%, CRC%, Pain intensity |
| Ahmedbeyli et al. (2014)  | CAF       | ADM              | ALLO               | AlloDerm, BioHorizon, USA                       | None               | -                   | None                | 29.8 ± 3.2           | 40.2 ± 6.8              | RD, CRC%, PD, CAL, WKG, Pain intensity |
| Zucchellie et al. (2014)  | CAF       | CTG              | AUTO               | Autologous                                     | None               | -                   | None                | 29.8 ± 3.2           | 40.2 ± 6.8              | RD, CRC%, PD, CAL, WKG, Pain intensity |

(Continues)
| Author and year          | Procedure | Test biomaterial | Type of biomaterial | Trade name - test | Control biomaterial | Type of biomaterial | Trade name - control | Surgery time (test) | Surgery time (control) | Outcomes assessed                  |
|-------------------------|-----------|------------------|---------------------|-------------------|--------------------|--------------------|----------------------|---------------------|------------------------|----------------------------------|
| Cardaropoli et al. (2014) | Modified CAF | CMX               | XENO                | Mucograft, Geistlich | None               | -                  | None                 | NR                  | NR                     | RD, PD, CAL, WKG, GT            |
| Alkan and Parlar (2013)  | CAF       | EMD               | XENO                | Emdogain®, Institut Straumann AG, Basel, Switzerland | CTG               | AUTO               | Autologous           | NR                  | NR                     | RD, RW, PD, CAL, RC%, WKG, GT    |
| Kuis et al. (2013)      | CAF       | CTG               | AUTO                | Autologous        | None               | -                  | None                 | NR                  | NR                     | PI, FMBS, PD, RD, WKG, CAL, RC%, CRC% |
| Kogon et al. (2013)     | CAF       | GF                | AUTO                | Autologous        | CMX               | XENO               | Collagen A.D         | NR                  | NR                     | PI, GI, PD, CAL, RD, RW, WKG, GT |
| Roman et al. (2013)     | CAF       | EMD               | XENO                | Emdogain®, Institut Straumann AG, Basel, Switzerland | CTG               | AUTO               | Autologous           | NR                  | NR                     | RD, RC%, CRC%, WKG             |
| Käser et al. (2013)     | CAF       | PCG               | BIO                 | Autologous        | CTG               | AUTO               | Autologous           | NR                  | NR                     | PI, GI, PD, CAL, RD, Pain Intensity, WKG |
| Cordaro et al. (2012)   | CAF       | EMD               | ALLO               | Emdogain®, Institut Straumann AG, Basel, Switzerland | None              | -                  | None                 | NR                  | NR                     | RD, PD, CAL, WKG, FMBS, PI      |
| Cardaropoli et al. (2012)| CAF       | CMX               | XENO                | Mucograft, Geistlich | CTG               | AUTO               | Autologous           | NR                  | NR                     | RD, PD, CAL, WKG             |
| Alkan and Parlar (2011) | CAF       | EMD               | ALLO               | Emdogain®, Institut Straumann AG, Basel, Switzerland | CTG               | AUTO               | Autologous           | NR                  | NR                     | RD, CAL, PD                   |
| Jankovic et al. (2010)  | CAF       | EMD               | ALLO               | Emdogain®, Institut Straumann AG, Basel, Switzerland | PRF               | BIO                | Autologous           | NR                  | NR                     | RD, PD, CAL, Pain Intensity    |
| Del Pizzo et al. (2005) | CAF       | EMD               | ALLO               | Emdogain Biora AB | None              | -                  | None                 | NR                  | NR                     | RD, RW, PD, CAL, WKG          |
| Spahr et al. (2005)     | CAF       | EMD               | AUTO               | Emdogain Biora AB | Placebo           | -                  | PGA                  | NR                  | NR                     | RD, RW, WKG, CAL, PD          |
| McGuire and Nunn (2003) | CAF       | EMD               | ALLO               | Emdogain Biora AB | CTG               | AUTO               | Autologous           | NR                  | NR                     | RD, RW, PD, CAL, WKG          |
| Hägglund et al. (2002)  | CAF       | EMD               | ALLO               | Emdogain Biora AB | Placebo           | -                  | PGA                  | NR                  | NR                     | RD, RW, WKG, CAL, PD          |
| Zucchelli et al. (1998) | CAF       | TLR               | ALLO               | Emdogain Biora AB | CTG               | AUTO               | Autologous           | NR                  | NR                     | PD, CAL, RD, RC%              |

Abbreviations: CAF- Coronally Advanced Flap, mCAF- modified Coronally Advanced Flap, PCM- Platelet concentrate matrix, CMX- Xenogenic Collagen Matrix, CTG- Connective Tissue Graft, EMD- Enamel Matrix Derivative, HA- Hyaluronic Acid, ADM- Acellular Dermal Matrix, PRF- Platelet Rich Fibrin, PRP- Platelet Rich Plasma, ADMA- Acellular Dermal Matrix(AlloDerm BioHorizons), ADMB- Acellular Dermal Matrix(Puros Dermis Zimmer Biomet), PPG- Periosteal Pedicle Graft, AFCC- Autologous Fibroblast Cell Culture, rh-PDGF-BB- recombinant human Platelet Derived Growth Factor-BB, GF- Gingival Fibroblasts, PCM- Platelet Concentrate Graft, GTR(R)- Resorbable Guided Tissue Regeneration Membrane, GTR(NR)- Non Resorbable Guided Tissue Regeneration Membrane, AUTO- Autologous Biomaterial, ALLO- Allogenic Biomaterial, XENO- Xenogenic Biomaterial, ALLP- Alloplastic Biomaterial, BIO- Biologic Biomaterial, RD- Recession Depth, RW- Recession Width, PD- Probing Depth, CAL- Clinical Attachment Level, WKG- Width of Keratinised Gingiva, RC%- Percentage of Root Coverage, FMBS- Full Mouth Bleeding Score, CRC% - Complete Root Coverage %, GTG- Gingival Thickness, PI- Plaque index, GI- Gingival Index, BOP- Bleeding on Probing, RES- Aesthetic score, NR- Not Reported.
CTG has always been considered as gold standard intervention for root coverage and for the modification of periodontal phenotype (Barootchi et al., 2020; Chambrone & Tatakis, 2015; Tatakis et al., 2015) because it demonstrates the best long-term maintenance of treatment (Pini Prato, Franceschi, et al., 2018). However, it presents with limitations such as increased surgical morbidity, bleeding and postoperative pain. Therefore, clinicians and the patients look for alternatives that can meet the clinical need and also improve the post treatment quality of life (Moraschini et al., 2019). In contrast, the use of CTG substitutes does not affect postoperative pain and quality of life (Rotundo et al., 2019; Tonetti et al., 2018). For this reason, the decision making to choose among different biomaterial substitutes in adjunct to CAF for root coverage of single or multiple gingival recessions must be based on scientific evidence.
Recently, the effect of time on the stability of postsurgical results emerged as an important factor for root coverage and periodontal procedures (Cortellini et al., 2017; Pini Prato, Magnani, et al., 2018; Wu et al., 2017). A duration of 6 months is considered as a sufficient time for healing and tissue stability after mucogingival surgery (Cheng et al., 2007) and some authors have shown that the data obtained at this time can already predict the results of 3 years of the RCP (Cairo et al., 2015; Jepsen et al., 2017), and at 12 months the maturation of the tissue after the procedure is already complete (Gurtner et al., 2008; Smith et al., 2015).

A data on long term effects of different RCP has been recently being reported (Moslemi et al., 2011; Pini Prato et al., 2011; Pini Prato, Franceschi, et al., 2018; Pini Prato, Magnani, et al., 2018; Rasperini et al., 2018) and although there are still some controversies, CTG-based techniques show the least changes over time (Pini Prato, Franceschi, et al., 2018; Rasperini et al., 2018). But, despite the fact that the evidence provides favorable results of early treatment (6 or 12 months) for gingival recessions (Francesco Cairo et al., 2014; Tavelli, Barootchi, et al., 2018), whether they persist for a longer time, has not yet been determined (Chambrone et al., 2019). In addition, a definitive conclusion cannot be drawn individually because of limited sample size and high drop outs (Chambrone et al., 2019; McGuire et al., 2012; Rasperini et al., 2018). Therefore, a time greater than 12 months, as a variable of the obtained treatment results, has never been explored. For this reason, this SR and NMA made direct and indirect comparisons between possible CTG substitutes with a minimum follow-up time of 12 months, avoiding any influence of extrinsic factors in the healing process. Furthermore, the incorporation of an NMA can provide information on the effect of time on the changes that occur in the results obtained postoperatively and at the same time the different substitutes of the CTG are compared.

One of the objectives of this article was to evaluate the effect of time on gingival recessions using the CAF as a flap design and comparing it with other biomaterials. Although it was found that the CAF + CTG and CAF + ADM + PRP approaches showed the best results in time for the percentage of root coverage, the CAF + CTG approach showed a greater difference in relation to the other approaches. These results are similar to those reported by other authors (Rasperini et al., 2018; Cairo et al., 2014; Dai et al., 2019) where they found that CAF + CTG have a tendency to displace gingival margin coronally, while CAF alone had a tendency towards apical relapse. It is
reported that, due to biological filler content of CTG, it has the ability to adapt flap on the root surface (Francesco Cairo et al., 2016) and increases the marginal thickness of soft tissue. This enables greater chance of achieving root coverage (Rebele et al., 2014). This is fundamentally crucial also for the stability of the gingival margin, since an increase in the thickness of the gingival tissue after a CTG has been associated with the effect of progressive adhesion over the years (Pini-Prato et al., 2010; Rasperini et al., 2018). Furthermore, it is also similar to that reported by Chambrone et al. (2019) and Mehta et al. (2019), where authors mention that there is, evidence suggesting that ADMs appear as the soft tissue surrogate that can provide the most similar results to those achieved by CTG for single or multiple recessions (Lee et al., 2002). On contrary, Leknes et al. (2005) did not find any difference in
time intervals between CAF and GTR for root coverage. It is suggested that a strict oral hygiene maintenance after each appointment, after the root coverage procedure was recommended (McGuire et al., 2014; Pini Prato et al., 2011; Zucchelli et al., 2018).

The importance of at least 2 mm KTW has been demonstrated as an important factor for the stability of the gingival margin over time (Pini Prato, Magnani, et al., 2018). Furthermore, it has also been suggested that KTW plays a crucial role in facilitating long-term maintenance of the patients themselves and reducing the risk of soft tissue relapse (Stefanini et al., 2018; Zucchelli et al., 2014).

In our analysis, we found that KTW was a significant predictor that greatly affected treatment slopes, which is also mentioned by Tavelli, Barootchi, et al. (2019) and Tavelli, Ravidà, et al. (2019). Among treatment approaches, CAF + PCM exhibited positive slopes for KTW increase in future recessions. A possible explanation could be the potential of this material to increase the width of the keratinized tissue (Yu et al., 2018). Despite all this, our results confirm that a CTG was the best treatment to increase KTW over time.

The SR included only data from RCTs, analyzing the best available evidence where different biomaterials were used as a complement to CAF (PCM, EMD, XADM, PRF, CMX, rhPDGF-BB + TCP, ADM, GTR (Bio), GTR (Non Bio), and CM). Furthermore, studies where there were smokers were not included, as smokers may have greater gingival margin instability than non-smokers (Raes et al., 2015) due to ecological, immunological and vascular deficiencies caused by tobacco use (Palmer et al., 2005).

**FIGURE 9** SUCRA ranking; 3E: Multi-dimensional scale ranking (MDS) for percentage of root coverage

**TABLE 4** GRADE analysis

| Comparison               | Network meta-analysis (quality evidence) | Pocket depth | Keratinized gingival width | Clinical attachment level | Recession width | Recession height | Overall  |
|--------------------------|------------------------------------------|--------------|---------------------------|--------------------------|----------------|-----------------|----------|
| CAF vs. CAF + PCM        | Low                                      | Low          | Low                       | Low                      | Low            | Low             | Low      |
| CAF vs. CAF + CTG        | Low                                      | Moderate     | Low                       | Moderate                 | Low            | Low             | Moderate  |
| CAF vs. CAF + EMD        | Low                                      | Low          | Moderate                  | Moderate                 | Low            | Low             | Moderate  |
| CAF vs. CAF + XADM       | Low                                      | Low          | Moderate                  | Moderate                 | Low            | Low             | Moderate  |
| CAF vs. CAF + PRF        | Low                                      | Low          | Moderate                  | Low                      | Low            | Low             | Moderate  |
| CAF vs. CAF + CMX        | Moderate                                 | Moderate     | Moderate                  | Moderate                 | Low            | Low             | Moderate  |
| CAF vs. CAF + rhPDGF-BB + TCP | Moderate                             | Moderate     | Moderate                  | Moderate                 | Moderate      | Moderate         | Moderate |
| CAF vs. CAF + ADM        | Moderate                                 | Moderate     | Moderate                  | Moderate                 | Moderate      | Moderate         | Moderate |
| CAF vs. CAF + GTR(Bio)   | –                                        | Moderate     | –                         | –                        | –              | –               | Moderate |
| CAF vs. CAF + GTR(Non Bio) | –                                    | Moderate     | –                         | –                        | –              | –               | Moderate |
| CAF vs. CAF + CM         | Moderate                                 | Moderate     | Moderate                  | Low                      | Moderate      | Low             | Moderate |
| Overall                  | Moderate                                 | Moderate     | Moderate                  | Moderate                 | Moderate      | Moderate         | Moderate |

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### FIGURE 10  Risk of bias summary for all included studies

| Study Reference | Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | Overall |
|-----------------|----------|----------|----------|----------|----------|----------|---------|
| Bankaitis et al. (2020) | + | + | + | - | + | + | + |
| Doerr et al. (2020) | + | + | + | - | + | + | + |
| Aydin et al. (2019) | + | + | + | - | + | + | + |
| Pilleri et al. (2019) | + | + | + | - | + | + | + |
| Voskdonat et al. (2019) | + | + | + | - | + | + | + |
| França–Grohmann et al. (2019) | + | + | + | - | + | + | + |
| Güler et al. (2019) | + | + | + | - | + | + | + |
| Malek et al. (2018) | + | + | + | - | + | + | + |
| Fonscolombi et al. (2018) | + | + | + | - | + | + | + |
| Kuca et al. (2018) | + | + | + | - | + | + | + |
| Mokashi et al. (2018) | + | + | + | - | + | + | + |
| Qattan et al. (2018) | + | + | + | - | + | + | + |
| Abou-Araj et al. (2017) | + | + | + | - | + | + | + |
| Jasani et al. (2017) | + | + | + | - | + | + | + |
| Cairo et al. (2016) | + | + | + | - | + | + | + |
| McGuire et al. (2016) | + | + | + | - | + | + | + |
| Lahsa et al. (2016) | + | + | + | - | + | + | + |
| Stefanini et al. (2016) | + | + | + | - | + | + | + |
| Lopez et al. (2015) | + | + | + | - | + | + | + |
| Cairo et al. (2015) | + | + | + | - | + | + | + |
| Minz et al. (2015) | + | + | + | - | + | + | + |
| McGuire et al. (2014) | + | + | + | - | + | + | + |
| Ahmadzadeh et al. (2014) | + | + | + | - | + | + | + |
| Zucchelli et al. (2014) | + | + | + | - | + | + | + |
| Gerdin et al. (2014) | + | + | + | - | + | + | + |
| Alsun et al. (2013) | + | + | + | - | + | + | + |
| Rades et al. (2013) | + | + | + | - | + | + | + |
| Kumar et al. (2012) | + | + | + | - | + | + | + |
| Chaudhuri et al. (2012) | + | + | + | - | + | + | + |
| Gerdin et al. (2012) | + | + | + | - | + | + | + |
| Alsun et al. (2011) | + | + | + | - | + | + | + |
| Jankovic et al. (2010) | + | + | + | - | + | + | + |
| Dol Phino et al. (2005) | + | + | + | - | + | + | + |
| Shahr et al. (2005) | + | + | + | - | + | + | + |
| McGuire et al. (2003) | + | + | + | - | + | + | + |
| Higgins et al. (1999) | + | + | + | - | + | + | + |

**Domain Definitions:**
- **Domain 1:** Randomization of participants
- **Domain 2:** Adequate sequence generation
- **Domain 3:** Blinding of participants and personnel
- **Domain 4:** Blinding of outcome assessment
- **Domain 5:** Incomplete outcome data
- **Domain 6:** Selective outcome reporting
- **Domain 7:** Other potential sources of bias

**Judgments:**
- **Low Risk:** No concerns
- **Moderate Risk:** Some concerns
- **High Risk:**严重的 concerns
- **Unclear Risk:** Unclear risk of bias
Some weaknesses of this study should be highlighted. First, most of the studies presented a high or moderate risk of bias, which increases the inconsistency of the results, leading to the fact that in the comparisons between CAF only with CAF with a biomaterial they presented a moderate GRADE analysis, thus decreasing, the recommendation of clinical results.

Another problem could be the differences in the process of making platelet concentrates. Variations in centrifuge type, speed, and G-force could change membrane patterns and, consequently, the number of growth factors and cytokines (Miron et al., 2019). Furthermore, the limited research and high risk of bias in these studies, mentioned by Li et al. (2019) and Moraschini and Barboza (2016), can make the interpretation of the results difficult.

Among the limitations of the literature, we observed that included RCTs provided no information regarding gingival phenotype of the patient at the start of the study or at follow-up intervals. Gingival phenotype was suggested to play a key role in determining future graft procedures, and this could not be explored with NMA. There was no significant added information from the analysis about gingival thickness (i.e., gingival thickness ≥ 0.8 mm or 1.2 mm has shown to be associated with greater chance of complete root coverage) (Baldi et al., 1999; Cairo et al., 2016). In addition, due to the lack of individual patient data, the impact of age and gender on the stability of the results was not investigated. However, in a recent article, age and gender were not found to be relevant factors in maintaining the stability of the gingival margin (Rasperini et al., 2018).

5 | IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE DIRECTIONS

Our SR and NMA found that ADM + PRP and PCM have the better clinical performance as an adjunct to CAF, for the percentage of root coverage and KTW, respectively, in the treatment of Miller’s class I and II gingival recessions (Cairo RT I). Based on the ranking of biomaterials, clinician will be able to make informed decisions in daily clinical practice. Standardization of the methods for using these biomaterials is essential to ensure that results are reproducible and predictable for monitoring long-term tissue stability and behavior.

6 | CONCLUSION

Our NMA found that CAF + CTG and CAF + PCM for KGW and CAF + CM + GF AND CAF + ADM + PRP for percentage of root coverage were ranked higher and would perform better in future clinical studies. The highest ranked material in improving CAL was CAF + ADM and CAF + PRF. In conclusion, CTG, ADM, and CM along with GFs showed improved stability for ≥12 months follow-up, when used in adjunct to CAF in terms of better percentage of root coverage and improved KGW. However, the overall evidence was moderate and therefore, well designed clinical trials are needed.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to the contents of this study.

AUTHORS CONTRIBUTION

Concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review, and guarantor: Sourav Panda, Shahnavaz Khijmatgar, Heber Arbildo-Vega, Abhaya Chandra Das, Manoj Kumar, Mohit Das, Leonardo Mancini, and Massimo Del Fabbro.

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

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