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ALLODERM IN MULTIPLE ADJACENT GINGIVAL RECESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Keywords:

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ABSTRACT: Objective: Gingival recession is one of the most common mucogingival defects for which patients seek periodontal therapy. Treatment options for gingival recession include surgical procedures with pedicle flaps, free soft tissue grafts, gingival veneering, restorations, *etc*. When multiple gingival recessions involving adjacent teeth are present, the first choice is to address all recession defects at one surgical time. This systematic review and meta-analysis aimed to compare the effectiveness of Alloderm over Connective Tissue graft (CTG) in managing multiple gingival recessions. **Methods:** A literature search with appropriate keywords was done with electronic databases *viz.* MEDLINE Ovid (from 1946 onwards); SCOPUS and EBSCO. (Multiple gingival recession) or multiple root coverage) and coronally advanced flap; (multiple gingival recession) or multiple root exposure) and connective tissue graft is the search term used. **Results:** Randomized controlled trials comparing Alloderm with CTG were included. The risk of bias of included studies was assessed, and metanalysis was done using Rev Man (VERSION 5.4). Of the 367 articles, only three went for meta-analysis. **Conclusion:** A statistically significant difference was shown in clinical outcomes of Alloderm compared with CTG at six months follow-up. Hence ADMA could be used as an alternative to the connective tissue graft.

INTRODUCTION: Periodontal disease is defined as chronic inflammation of supporting tissues of teeth caused by microorganisms or a group of microorganisms leading to the destruction of the periodontal ligament, cementum, and alveolar bone resulting in pocket depth, gingival recession or both [1]. The recent Global Burden of Disease showed that severe periodontitis is the 11th most prevalent disease among the world population [2]. One of the most common mucogingival defects for which patients seek to have esthetic concern is gingival recession [3].

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Tissue inflammation caused by bio-film accumulation or traumatic brushing, aberrant frenum, abnormal bone anatomy, traumatic tooth brushing, anatomical variations (fenestrations, dehiscence, abnormal tooth position), thin gingival morphology, post orthodontic treatment, high muscle attachment, use of Smokeless tobacco are some of the reasons related to the pathogenesis of gingival recession [4].

This clinical condition is common in the general population and may result in esthetically unfavorable effects and increased susceptibility to root caries and dentine hypersensitivity. The various treatment options for correcting gingival recession include surgical procedures with pedicle flaps, free soft tissue grafts, gingival veneering, restorations, *etc*. Periodontal plastic surgery aims to cover the recession defect with improved esthetic

results related to adjacent soft tissues and minimal probing depth (PD). The above procedure is indicated when the clinical condition relates to esthetic problems, dentinal hypersensitivity, root caries, or hinders with proper plaque removal [5]. Soft tissue flaps, associated with or without autograft or allograft, have been used to address gingival recession and show high predictability regarding root coverage [6, 7]. Reliability of the proximal bone is essential to determine the predictability of outcomes in terms of root coverage, irrespective of the surgical technique used [8].

Langer and Langer [6] introduced subepithelial connective tissue graft (SCTG), in which connective tissue graft combined with a superimposing pedicle graft was used. The coronally positioned flap (CPF) [8] is one of the most effective techniques for treating gingival recession, the unpredictability of long-term defects led to the incorporation of additive materials like connective tissue grafts (CTG) along with CPF. This treatment option of CTG with CPF is considered the gold standard for gingival recession management [7, 9, 10]. But in multiple gingival recessions, the limited tissue availability and need for a second surgical site led to the introduction of other graft materials like sclera, dura mater, and freeze-dried skin grafts. However, using these materials did not result in tissue identical to that of host tissue [11].

An acellular dermal matrix allograft (ADMA, ADM, ADMG), a human soft tissue chemically processed, immunologically inert, acts as a porous structure, upkeeps the migration of fibroblasts and revascularization [12]. Ultrastructural integrity of the acellular matrix is well maintained, thus avoiding induction of inflammatory response. The basal membrane is maintained to facilitate the migration and retention of epithelial cells. It exhibits undamaged collagen and elastin matrices and does not initiate an inflammatory response by the host recipient tissue. As it undergoes an inflexible process to render it sterile, it is devoid of any bacterial and viral contamination [8, 12]. The first reported use of ADMA in gingival grafting for root coverage was in 1994 [13]. Since, then, it has been used in many types of periodontal plastic surgery, including the treatment of alveolar ridge deficiencies, guided tissue regeneration, and the alteration of gingival pigmentation, [14] increased mucosal width around implants [15]. The reported root coverage using ADMA is more than 90% [9] while others have reported 60 to 80% [5, 16]. One problem that may obstruct the use of the acellular graft would be excessive shrinkage [17]. The free gingival graft shrinkage varies between 30 and 50% [15]. However, no study is evaluating how the acellular graft would shrink over time. The use of ADMA with coronally advanced flap had shown predictable results in treating isolated gingival recessions, increasing keratinized gingival [18, 19, 20].

Although systematic reviews that evaluate the use of ADMA exist, they are wide in scope and include all major root coverage procedures together. The first study limited to ADMA concluded that ADMA had no significant influence in improving periodontal clinical parameters compared to conventional mucogingival surgeries [20]. The gold standard for root coverage procedures considered are Connective tissue grafts but due to the limited tissue availability in multiple adjacent gingival recessions, there has been an extensive search for alternatives [21]. Chambrone *et al*.'s 2008 [22,] in their systematic review, found SCTG to be superior in the management of gingival recession. A systematic review conducted by the same authors has not found a statistically significant difference between SCTG and ADMG and attributed the finding to a small number of RCTs including [23].

A systematic review by Chambrone *et al*.'s 2015 found similar improvement in clinical parameters for ADMG and SCTG; however, the review argued for the superiority of SCTG [24]. A meta-analysis by Gapski *et al*.'s 2005 [19] concluded that no differences were observed between the treatment modalities regarding gingival recession coverage and KT gains; they could not analyze clinical attachment gain. Sarah Ivy Gallagher *et al.* [25] concluded that ADMG would be a suitable root coverage substitute for an SCTG when avoidance of the second surgical site is prepared. No previous systematic review could make strong comparisons between the SCTG and the ADMG. Based on literature support, it was planned to conduct a systematic review and meta-analysis of acellular dermal matrix allograft over conventional gingival autografts in adult patients with Miller's Type I and II multiple adjacent gingival recessions.

MATERIAL AND METHODS:

Study design: This systematic review was done by PRISMA guidelines.

Search Strategy: The searches were performed in Pubmed/Medline and Scopus databases for articles published up to and including February 2019, without language restrictions. For PubMed/ Medline, combinations of Medical Subject Headings (MeSH) terms, keywords, and free terms were utilized. A hand search was also performed based on the bibliographic details of the included studies. The review protocol was prospectively registered with PROSPERO (CRD42018096814).

Key Words Used in Search Strategy: The search strategy was customized appropriately for each of the additional databases being used, considering differences in controlled vocabulary and syntax rules. The search terms were as follows (multiple gingival recession) or multiple root coverage) and coronally advanced flap; (multiple gingival recession) or multiple root exposure) and connective tissue graft; (multiple gingival recession) and acellular dermal matrix allograft) and connective tissue graft; (multiple gingival recession) and alloderm; (coronally advanced flap) and alloderm; (multiple gingival recession) and coronally advanced flap) and alloderm; (multiple root exposure) and coronally advanced flap; (multiple gingival recession) and coronally advanced flap) and acellular dermal matrix allograft. In addition, the references of any potential clinical trials and prior systematic reviews were examined to identify any relevant studies not found through the database search.

Screening of the Recovered Articles: Titles and abstracts of studies identified according to the inclusion criteria were screened independently by the 2 reviewers (SR and RV). The reviewers evaluated Selected full-text studies independently using the selected criteria. Any disagreements were settled through discussion.

Inclusion Criteria: This systematic review was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26]. To define a patient-centered clinical inquiry, we also developed a well-built protocol of population, intervention, comparison, and outcomes (PICO) [27] format in this systematic review. We included RCTs with a minimum of six months of follow-up. The other inclusion criteria are listed below, following the Participants, Interventions, Comparisons and Outcomes framework. Patients with Miller's class I or II gingival recessions were included (Participants). The following surgical procedures for root coverage were considered: CAF with CTG, and CAF with ADM (interventions). Intervention is of soft tissue grafting for treating Miller's class I and II gingival recession as a root coverage procedure. The effectiveness of an acellular dermal matrix allograft is compared with another conventional gingival autograft for root coverage procedures. Control groups included studies with CPF or CAF and CTG/SCTG for root coverage procedures.

Exclusion Criteria: Those studies whose follow-up period was less than six months and those studies comparing effectiveness of alloderm with other gingival augmentation procedures.

Outcomes Evaluated: The primary outcome was the amount of root coverage (Percentage), changes in the width of keratinized tissue (mm) and secondary outcomes included changes in clinical attachment level (mm) and probing pocket depth (mm).

Data Extraction: For each included study, both reviewers (SR and RV) independently extracted and recorded the data regarding the setting, population, intervention, comparison, outcomes, and study design. The authors were contacted for missing data.

Risk of Bias: The risk of bias for each included study was assessed using the Cochrane Risk of Bias tool for randomized controlled clinical trials consisting of six domains *viz.* selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias [28].

Synthesis of Findings: Study outcomes reported in more than one study were analyzed using Review Manager (RevMan) version 5.3. The Mean Differences with 95% confidence intervals were calculated for continuous variables. The level of statistical significance was set at $p<0.05$. The random-effects model for heterogeneity was used.

Heterogeneity was evaluated using the I2 statistical tests.

RESULTS:

Study Selection: The flowchart of how the search results were analyzed is shown in **Fig. 1.** A total of 367 articles were retrieved after the database search. After removal of duplicates (n=63), 304 articles remained. Among them, 153 were excluded as they were non-RCTs. Among the remaining 151 articles which were screened for title and abstracts, 132 were excluded as they were irrelevant to the current review objectives. Nineteen articles were thus included for full-text screening, of which 16 articles were excluded as they did not meet the inclusion criteria. Thus a total of 3 articles were included for qualitative and quantitative synthesis.

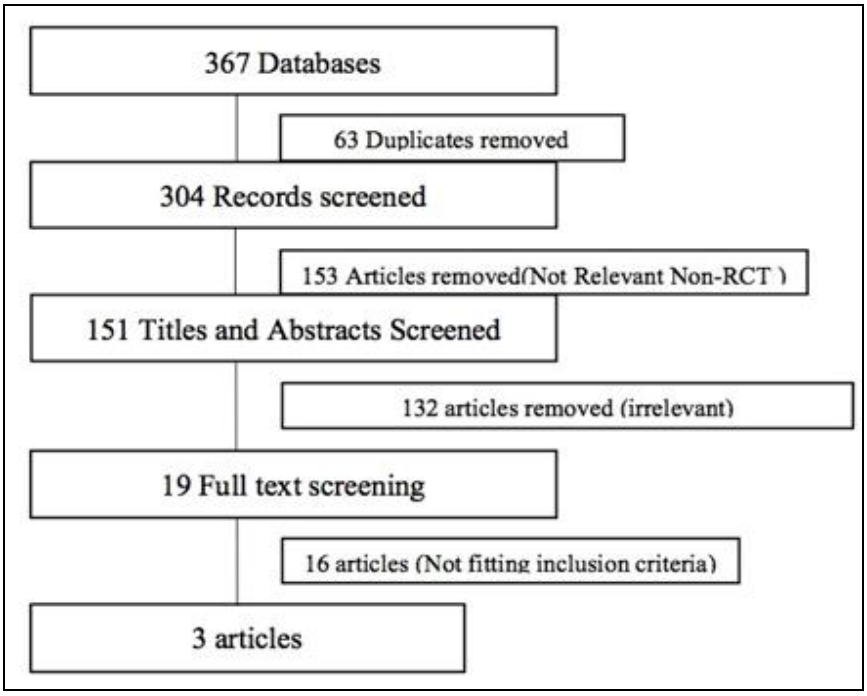

FIG. 1: FLOW CHART SHOWING THE SCREENING AND SELECTION PROCESS

Characteristics and Quality Assessment of the Included Studies: The characteristics of the included studies are presented in **Table 1**. Two studies used a parallel-group design, and one study employed split-mouth models. The number of participants ranged from seven to 30 patients. Of the three articles, two reported the outcomes of Root coverage gain (RC), reduction in probing pocket depth (PPD), gain in clinical attachment level (CAL), and gain in width of keratinized tissue (KT); one study [28] reported all the outcomes except root overage gain. The follow-up period of the studies ranged from three to 6 months.

TABLE 1: CHARACTERISTICS OF INCLUDED STUDIES

Study ID	Methods	Study length	Participants	Surgical methods	Outcome
Haghehati *et al* 2006, [29]	RCT, split-mouth	6 months	9 participants, Miller's class I or II multiple recessions of at least 2mm	ADMA,CTG (the basement membrane (white) side of the material was placed facing up towards the flap); No root conditioning	(ΔPPD), (ΔCAL), (ΔGR), (ΔKG).
Somnath *et al* 2012,[40]	RCT, parallel design	6 months	10 participants; Miller's class I or II multiple recessions of at least 2mm	ADMA, SCTG (CT side toward flap); releasing incisions; no root conditioning	(ΔPPD), (ΔCAL), (ΔGR), (ΔKG).
Thakare *et al* 2015[42]	RCT, parallel design	6 months	30 participants; Miller Class I or II multiple recessions of at least 2 mm	CTG, ADMG (CT side toward flap); releasing incisions; no root conditioning	ΔKT, ΔCRC ΔPRC , ΔCAL

Risk of Bias within and Across Studies: Fig. 2A and **2B** show the risk of bias across the studies and within studies. The assessment of bias risk indicated a high risk in the included studies. The blinding of participants, personnel, and outcome assessment was not followed or reported in any of the included studies.

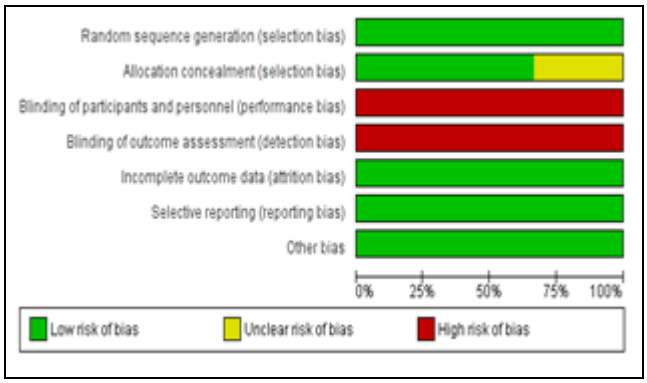

FIG. 2A: RISK OF BIAS ACROSS STUDIES

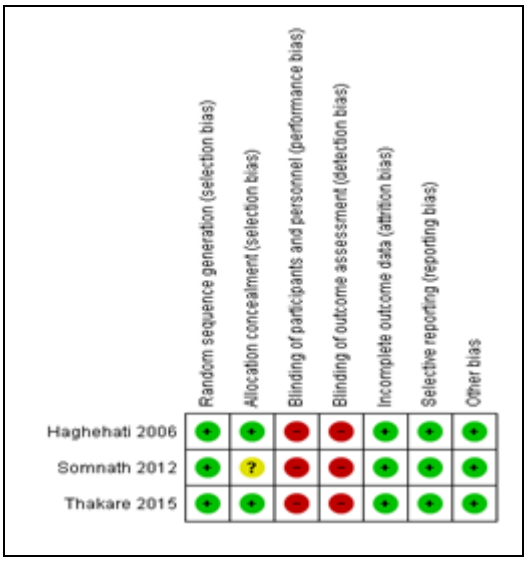

FIG. 2B: RISK OF BIAS WITHIN STUDIES

Meta-analysis: The results of our meta-analysis are presented in four forest plots **Fig. 3A-D.** Studies were evaluated for randomization, masking, and inclusion of control comparison and analyzed the differences in baseline measurement. And presented treatment outcomes at a range of follow-up points, including months. Since, different follow-up durations may have influenced the findings regarding clinical outcomes, we pooled the results at minimum of six months of follow-up.

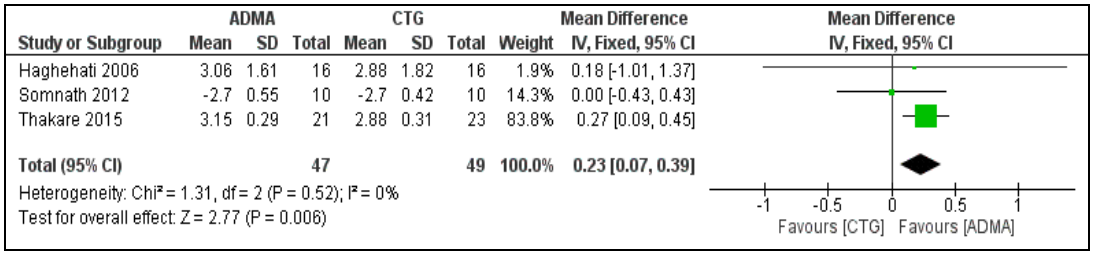

FIG. 3A: CLINICAL ATTACHMENT LEVEL

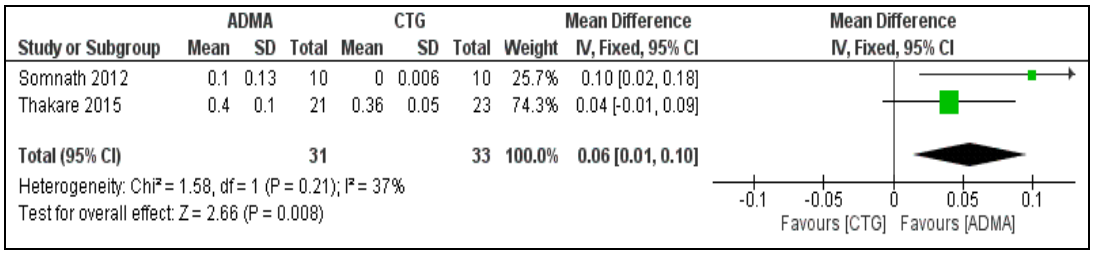

FIG. 3B: PROBING POCKET DEPTH

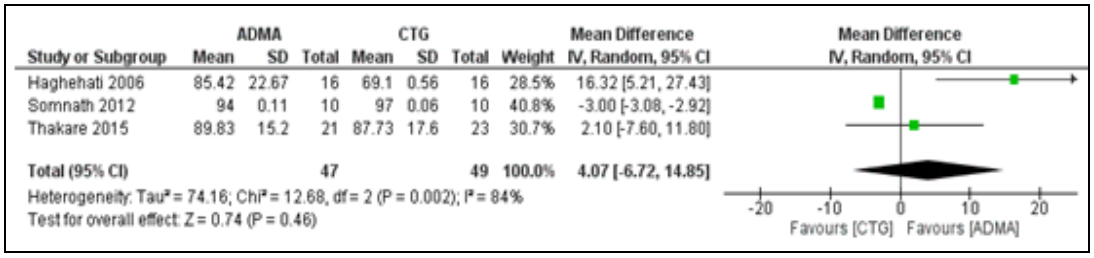

FIG. 3C: ROOT COVERAGE

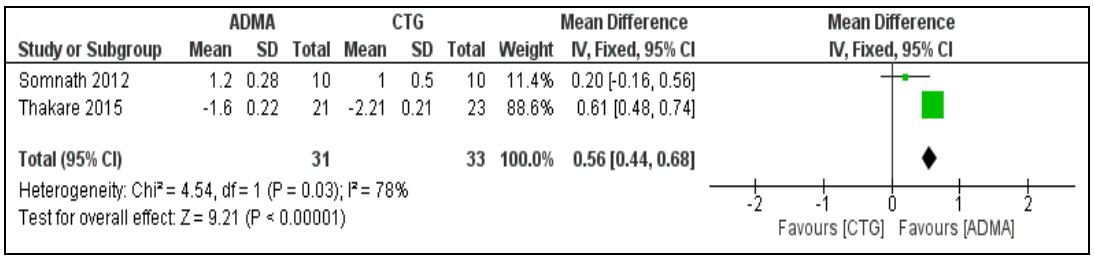

FIG. 3D: WIDTH OF KERATINIZED GINGIVA

ADMA-Based Root Coverage versus Other Conventional Surgical Procedures: Root coverage values were obtained from three studies, and an overall Mean Difference (MD) was found to be favoring ADMA. However, the results were not statistically significant [MD 4.07% (95% CI -6.72, 14.85) p = 0.46] **Fig. 3C.**

ADMA-Based Changes in Probing Pocket Depth versus Other Conventional Surgical Procedures: ADMA-Based Changes in Probing Pocket Depth versus Other Conventional Surgical Procedures: The effect on probing pocket depth was evaluated by two studies and the difference was statistically significant and favoring ADMA [MD 0.06 (95% CI 0.01, 0.10) p=0.008] One study did not provide post intervention values for pocket depth and hence was not included for meta analysis **Fig. 3B.**

ADMA-Based Changes in Clinical Attachment Level Versus Other Conventional Surgical Procedures: Three studies evaluated the effect of ADMA and other connective tissue grafts (CTG) on Clinical Attachment Level. It was observed that the Mean Difference (MD) was 0.23 [(95% CI 0.07, 0.39) p = 0.006] was statistically significant, favoring ADMA **Fig. 3A.**

ADMA-Based Changes in Width of Keratinized Gingiva Versus Other Conventional Surgical Procedures: There was a statistically significant difference in the width of keratinized gingiva favouring ADMA based on results obtained from two studies [MD 0.56 (95% CI 0.44, 0.68) p < 0.0001] **Fig. 3D.**

DISCUSSION: The focused question of this meta-analysis was whether there were any clinical outcomes of CAF with ADM in treating Miller's I or II multiple adjacent gingival recession compared to the reference treatments of CAF combined with CTG? Earlier evidence confirmed that CAF with CTG resulted in better clinical outcomes than CAF alone, with no other therapies providing better results than CAF with CTG [21]. An acellular dermal matrix allograft (ADMA, ADM, ADMG, Alloderm) Life Cell, Inc. was used as an alternative treatment for mucogingival surgical procedures [12]. Alloderm is double-sided and available in various sizes, multiple sites can be treated during one surgery appointment. The basal lamina side is compatible for repopulation by epithelial cells. The connective tissue side allows for the migration of fibroblasts and blood vessels [30]. Some authors argue that the orientation of the ADM affects the outcome of periodontal plastic procedures [9]. However, there were no differences in clinical outcomes when comparing the basal lamina side against the tooth and the connective tissue side against the tooth [31]. SCTG/CTG and ADMA (ADMG) differ in their healing processes. As SCTG is an autograft, it endures through anastomoses between the graft's vessels and those of the recipient site [12]. Hence, the flap does not need to cover the connective tissue graft completely. In contrast, nonvital ADMA depends entirely on migrating host cells and vessels for nutrition and repair. It depends on direct contact between the graft and the flap, and thus, it requires complete coverage with a tensionless flap. Exposure of ADMA may result in partial failure of the graft [7].

Due to these differences, different surgical techniques are available for ADMA than those Langer and Langer had proposed for SCTG, including broader flaps, with or without vertical releasing incisions, to allow for a greater blood supply and thus, greater access to nutrition and cells [32, 33]. The resulting mucosa is histologically similar in SCTG and ADMA [9, 20]. There is complete incorporation of the graft without any gross inflammatory reaction. Hence, the ADMA does not initiate a foreign body reaction, root resorption and ankylosis [20, 34].

In both SCTG and ADMA, the interface consists of a long junctional epithelium coronally and connective tissue attachment apically. The abundance of elastin in ADMA, which is retained after incorporation of the graft, allows for its histological differentiation from the surrounding tissues because elastin is not a primary component of human gingival [4].

The overall results of this meta-analysis revealed that (ΔPPD), (ΔCAL), (ΔRC), (ΔWKG) were slightly higher in the CAF with ADM group than in the CAF with CTG group but not to statistically significant. In deeper periodontal pockets, pocket depth reduction is usually associated with tissue shrinkage due to a reduction in inflammation or a gain in CAL following periodontal therapy. The mechanism by which ADMA could increase KT has not been identified. ADMA allograft was less productive and less predictable than the autogenous FGG in increasing attached keratinized tissue due to considerable shrinkage [35, 5].

Histologically sections of ADMA and FGG-treated sites suggested that the resultant tissues of ADMA grafts were similar to scar tissue and could not direct cytodifferentiation of the covering epithelium [36]. Root coverage values were obtained from three studies, and an overall Mean Difference (MD) was found to be favouring ADMA. However, the results were not statistically significant. Alloderm tended to break down in the long term, while the long-term results with an SCTG tended to remain stable [7]. The CTG was found to influence epithelial behaviour through the secretion of paracrine growth factors like keratinocyte growth factor, direct contact and communication through the basement membrane [5, 16, 7, 37].

Keratinization of ADMA takes longer than SCTG [14, 37, 39]. However, this could not be evaluated in this meta-analysis. ADMA vascularizes *via* preserved channels, acts as a barrier, and integrates into host tissues. ADMA and CTG seemed to be well integrated into a single highly vascularized structure, indicating almost complete incorporation of ADMA [20]. Interestingly, our meta-analysis favored ADMA in terms of PPD reduction, CAL gain, and keratinized gingival width. This is concurrent with the findings of three included studies, which found that ADMA and CAF had an advantage with all clinical parameters [40, 29, 41]. The included studies were Haghehati 2006 *et al* [29]., *Somnath et al.* 2012 [30], Thakare *et al.* 2015 [42]. Haghehati *et al.* [29] showed a mean root coverage OF 85.4% for ADMA and 69% for SCTG; the results tended to favour the ADMA procedure.

Uniform thickness of ADMA compared to connective tissue grafts obtained from the palate may result in the better adaptation of the graft over the exposed root and graft material. ADMA could be useful for root coverage in cases with shallow recession depths. The gain in clinical attachment level could not be justified because of the absence of histological evidence regarding healing. Somnath *et al.* [40] showed a 97% mean root coverage in the SCTG and the ADMA group was 94%.

The mean gain in clinical attachment level in both groups was 2.7mm. ADMA may also act as a barrier equivalent to a selective cell repopulation membrane, thus encouraging periodontal-guided tissue regeneration. The width of keratinized gingiva in the SCTG group was 1.2 mm and 1 mm in the ADMA group. The difference could be attributed to considerable ADMA shrinkage during the healing phase. Thakare [42] had shown that, on comparing the root coverage obtained using CAF and ADMA and CAF and SCTG, greater coverage was obtained in CAF + ADMA (89.83%) group when compared to CAF + SCTG (87.73%). According to this author, the clinical changes probably represented a combination of new connective tissue attachment in the apical half of the defect and long junctional epithelium in the coronal half.

All the treatment groups resulted in a significant increase in the WKT. The CAF + SCTG showed a significantly greater increase in the WKT of 2.21 mm compared to CAF + ADMA (1.6 mm) and CAF (1.00 mm) groups.

In deeper periodontal pockets, pocket depth reduction is usually associated with tissue shrinkage due to reduced inflammation or a gain in CAL following periodontal therapy. ADMA allograft was less effective and less predictable than the autogenous FGG in increasing attached keratinized tissue due to graft shrinkage [11, 5].

Histologically, the microstructure of ADMA and FGG treated sites suggested that the resultant tissues at ADMA grafted sites were similar to scar tissue and could not direct cytodifferentiation of the covering epithelium [43].

Root coverage values were obtained from three studies, and an overall Mean Difference (MD) was found to be favouring ADMA. However, the results were not statistically significant. Studies have shown that keratinization of ADMA takes longer than SCTG [10, 38, 39]. But, this could not be evaluated in this meta-analysis. ADMA re-vascularizes *via* preserved channels, acts as a barrier, and it integrates into host tissues. ADMA and CTG seemed to be well integrated into a single highly vascularized structure, indicating almost complete incorporation of ADMA [20]. However, some studies have shown that Alloderm tends to break down in the long term, while the long-term results with an SCTG remain stable [32]. The CTG was found to influence epithelial behavior through the secretion of paracrine growth factors like keratinocytes growth factor, direct contact, and communication through the basement membrane [5, 16, 7, 37].

Risk of bias showed a high risk of bias among included studies. Blinding of participants and personnel was not done, probably due to the nature of the study's intervention. Blinding of outcome measures could have been included in the study, which is one of the limitations of the present study. Each included study was university-based and thus was conducted under ideal conditions. Hence, the applicability to clinical situations is limited. Many of the studies had significant sources of bias; for example, the description of the randomization method was inadequate in some cases. No histological evaluations were conducted. As only one RCT evaluated relapse of isolated root coverage, the stability of ADMA needs to be measured with longer-term follow-ups [44]. Additional research would also be beneficial, particularly into patient-based outcomes, including post-operative discomfort, color match (aesthetic score index), and satisfaction. After efficacy, this information should be a major consideration in the decision-making process.

CONCLUSION: The present systematic review and meta-analysis show a difference between the clinical outcomes of the two treatment modalities; CAF, SCTG, CAF, and ADMA. In conclusion, ADMA can be used in case of reduced gingival thickness for patients with multiple gingival recessions and helps the clinician to save operative time.

ADMA can be suggested as a clinical modality for whom the additional cost is not a barrier and who would prefer not to have a second surgical site. In the future, clinical trials on ADMA focused on complications such as ADMA exposure; manner of placement of ADMA, its comparison with other mucogingival approaches like platelet-rich fibrin, living cell construct, labial submucosal tissue (LST), *etc*. and choice of appropriate surgical technique and longer follow up period would serve as the base of a pyramid over which strong evidence can be built.

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CONFLICTS OF INTEREST: The authors do not have any financial interest in the companies whose materials are included in this article.

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