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REVIEW

Use of platelet-rich fibrin for the treatment of gingival recessions: a systematic review and meta-analysis

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Abstract

Objectives The aim of this systematic review and meta-analysis was to compare the use of platelet-rich fibrin (PRF) with other commonly utilized treatment modalities for root coverage procedures.

Materials and methods The eligibility criteria comprised randomized controlled trials (RCTs) comparing the performance of PRF with that of other modalities in the treatment of Miller class I or II (Cairo RT I) gingival recessions. Studies were classified into 5 categories as follows: (1) coronally advanced flap (CAF) alone vs CAF/PRF, (2) CAF/connective tissue graft (CAF/CTG) vs CAF/PRF, (3) CAF/enamel matrix derivative (CAF/EMD) vs CAF/PRF, (4) CAF/amnion membrane (CAF/AM) vs CAF/PRF, and (5) CAF/CTG vs CAF/CTG/PRF. Studies were evaluated for percentage of relative root coverage (rRC; primary outcome), clinical attachment level (CAL), keratinized mucosa width (KMW), and probing depth (PD) (secondary outcomes).

Results From 976 articles identified, 17 RCTs were included. The use of PRF statistically significantly increased rRC and CAL compared with CAF alone. No change in KMW or reduction in PD was reported. Compared with PRF, CTG resulted in statistically significantly better KMW and RC. No statistically significant differences were reported between the CAF/PRF and CAF/EMD groups or between the CAF/PRF and CAF/AM groups for any of the investigated parameters.

Conclusions The use of CAF/PRF improved rRC and CAL compared with the use of CAF alone. While similar outcomes were observed between CAF/PRF and CAF/CTG for CAL and PD change, the latter group led to statistically significantly better outcomes in terms of rRC and KTW. In summary, the use of PRF in conjunction with CAF may represent a valid treatment modality for gingival recessions exhibiting adequate baseline KMW.

Clinical relevance The data indicate that the use of PRF in conjunction with CAF statistically significantly improves rRC when compared with CAF alone but did not improve KMW. Therefore, in cases with limited baseline KMW, the use of CTG may be preferred over PRF.

Keywords Gingival recession · Periodontal plastic surgery · Platelet-rich fibrin · L-PRF

Introduction

Studies conducted in the USA have now demonstrated that approximately 90% of the population reports having at least one tooth with a 1-mm recession by age 60, with up to 40% displaying recessions greater than 3 mm [1, 2]. The ultimate goal of root coverage procedures is a resolution of the defect by providing complete root coverage, with ideal keratinized and attached tissue with a seamless esthetic transition with neighboring tissues [3]. Multiple periodontal plastic surgical procedures with a variety of biomaterials have been proposed to correct these mucogingival deformities and thus rebuild the

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lost attachment apparatus. Traditionally, connective tissue grafts (CTGs) from the palate in combination with different flap designs have been utilized. Nevertheless, alternative treatment options, including various biomaterials and/or bioactive agents, have been proposed over the years with the aim of lowering patient morbidity [3, 4].

A variety of collagen-based membranes and dermal tissue derivatives from either allograft or xenograft origin have been brought to market for the management of gingival recessions. While these substitute materials provide an excellent three-dimensional matrix for the migration and proliferation of fibroblasts, reported disadvantages have included limited regenerative potential as well as a lack of long-term keratinization of tissues within the grafted regions [5]. In an attempt to increase the bioactivity of barrier membranes, a variety of commercial membranes derived from placental tissues (amnion) have recently been brought to market, although long-term clinical data remain scarce [6, 7].

Similarly, another strategy has been the use of regenerative growth factors, either utilized alone or in combination with collagen membranes or CTGs, to stimulate the regenerative potential of fibroblasts within the defect area. A commonly utilized bioactive agent for the treatment of gingival recessions has been the use of enamel matrix derivative (EMD) derived from porcine origin. Results from animal and human studies have shown that EMD leads to positive clinical and histological outcomes when combined with a coronally advanced flap (CAF) procedure [8, 9]. Similarly, the use of recombinant human growth factors such as rhPDGF (Gem21) has also been successfully utilized in the treatment of gingival recessions [10, 11].

Over the past decade, blood concentrates have been proposed as a means to further speed tissue regeneration in dentistry and medicine. Originally, platelet-rich plasma (PRP) was utilized as the first-generation blood concentrate with widespread use, particularly in the field of maxillofacial surgery [12]. Over time, one of the reported drawbacks included its use of anticoagulants, or known inhibitors of clot formation, thereby decreasing the long-term release of growth factors and ultimately diminishing its regenerative potential [13]. For these reasons, the use of PRP has gradually decreased over the years, and its application in root coverage and mucogingival procedures has never been well adapted during routine periodontal surgical procedures.

Platelet-rich fibrin (PRF) has since been developed as a second-generation platelet concentrate to avoid anticoagulants [14–18]. Following centrifugation, a fibrin-dense membrane is produced with entrapment of host platelets and leukocytes shown to favor the slow and gradual release of growth factors. A number of systematic reviews have thoroughly documented the use of PRF in regenerative dentistry, where it has been shown to particularly favor soft tissue healing over hard tissue healing [16, 19, 20]. Furthermore, the use of PRF has also been evaluated for root coverage procedures in randomized clinical studies [16, 21, 22]. Therefore, the aim of this systematic review and meta-analysis was to evaluate the current evidence regarding the use of PRF for the treatment of Miller class I or II gingival recessions [23] in comparison with other treatment options.

Materials and methods

Protocol and registration

This systematic review was undertaken by following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [24], and the PRISMA [25] checklist, in order to increasing the quality and transparency of the study reporting. The review was recorded in the PROSPERO database under number CRD42019139709.

Focused question (based on PICO criteria) [26]

In patients with Miller class I or II (or Cairo RT I) [27, 28] gingival recession (P), is the use of PRF (I) beneficial as compared with other treatment options (C), in terms of extent of root coverage and other clinical outcomes (O)?

Outcome measures

The primary outcome variable was the change in the percentage of relative root coverage (rRC). The secondary outcome variables were clinical attachment level (CAL), keratinized mucosa width (KMW), and pocket depth (PD).

Search strategy

Electronic searches were conducted in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, and Embase for articles that were published until September 2019 without restrictions on dates or language. In addition, manual searches of the following journals were performed: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *Journal of Periodontal Research*, and *International Journal of Periodontics & Restorative Dentistry*. A search of the gray literature through the Literature Report [29] and OpenGrey databases [30] was also conducted. Finally, we evaluated the reference lists (cross-referencing) of all previous reviews and potentially included studies using MeSH terms, keywords, and other free terms related to the following: "gingival recession," "gingival recessions," "keratinized gingiva," "Miller Class I," "Miller Class II," "plastic surgery," "periodontal plastic surgery," "mucogingival surgery," "muco-gingival surgery," "root coverage," "platelet-rich fibrin," and "PRF."

Eligibility criteria and study selection process

This systematic review included RCTs and prospective controlled trials with follow-up periods of ≥ 6 months comparing the performances of CAF/PRF with CAF alone or in combination with other biomaterials (CAF/biomaterial) in patients with Miller class I or II (or Cairo RT I) gingival recessions [23, 28].

The exclusion criteria included animal studies, retrospective cohort studies, in vitro studies, case series, case reports, and reviews. In addition, studies of volunteers with decompensated metabolic disorders or active periodontal disease were also excluded. All studies included the use of PRF produced in a centrifuge in standard silica-coated plastic tubes and/or glass tubes.

The process of searching for and selecting the studies was conducted in duplicate by two authors (RJM and VM). First, the titles and abstracts were carefully evaluated, followed by the thorough assessment of the potential articles according to the eligibility criteria of this SR. Possible disagreements were resolved when the two authors reached a consensus.

Data synthesis

The following data, when available, were extracted from the included studies: authors, study design, follow-up, number of treated recessions, number of subjects, age range, gender, number of smokers, Miller class, site of recessions, surgical technique, rRC, CAL, KMW, PD, centrifugation system, volume of blood drawn, and centrifugation parameters. Each of the included randomized clinical trials was then grouped into one of the following 5 categories: (1) CAF alone vs CAF/PRF, (2) CAF/CTG vs CAF/PRF, (3) CAF/EMD vs CAF/PRF, (4) CAF/AM vs CAF/PRF, and (5) CAF/CTG vs CAF/CTG/PRF.

Assessments of the risk of bias

The risk of bias analysis was performed by two reviewing authors (RJM and VM). The Cochrane Collaboration's tool for assessing risk of bias [31] was used for RCTs. Each study was analyzed in relation to six criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Studies were classified as having a low, medium, or high risk of bias when they met all, all but one, or all but two or more criteria, respectively.

Statistical analysis

The continuous variables (rRC, CAL, KMW, and PD) of the included studies were categorized into groups and analyzed in a meta-analysis using Review Manager software (version 5.2.8, Copenhagen, Denmark, 2014).

The estimates of the intervention effects (mean difference) were expressed as percentages or millimeters with 95% confidence intervals (CIs). The inverse variance method was used for the random effects or fixed effects models, depending on the heterogeneity between the studies. Heterogeneity was assessed using chi-square tests. Values ≤ 25%, > 25%, ≤ 50%, and ≥ 50% were classified as indicating, respectively, low, moderate, and high heterogeneity. The use of the random effects model was conducted when heterogeneity was found. In contrast, the fixed effects model was used in cases of low or moderate heterogeneity. The statistical significance level of the effect of meta-analysis was fixed at $P \leq 0.05$.

A funnel plot was drawn for the primary outcome variable to assess publication bias across studies.

Results

Literature search

The initial search produced 752 titles from MEDLINE/PubMed, 72 from the Cochrane Central Register of Controlled Trials, 69 from the Web of Science, and 83 from EMBASE. After the first evaluation (title and abstract assessment), 976 articles were excluded. Of the 24 potential articles, 7 studies [32–38] were excluded after careful reading of the full text because they did not meet the inclusion criteria. Consequently, 17 studies [39–55] published between 2009 and 2019 were included in this SR. The reasons for the exclusion of potential studies and the search and selection processes are presented in Supplemental Fig. 1.

Characteristics of included studies

The characteristics of the included studies are presented in Table 1. Seventeen RCTs [39–55] (eleven [39, 44–46, 48–52, 54, 55] with a parallel design and six [40–43, 47, 53] with a split-mouth design) were included. The number of participants in the studies ranged from 10 [45] to 40 [54], with an average age of 36 ± 2.93 years. A total of 831 (432 test and 399 control) gingival recessions were treated. All of the studies focused on single or multiple Miller class I or II (or Cairo RT 1) recessions. Two studies [40, 41] analyzed only teeth from the anterior maxillary region. The follow-up period ranged from 6 months [39, 41–44, 46–49, 51–55] to 12 months [40, 45, 50] (mean, 7.05 months). The majority of articles investigated CAF/PRF as the test group, while the control groups used CAF alone [39, 43, 44, 46, 48, 50, 51, 53], in combination with CTG [41, 42, 45, 47–49, 52, 54], EMD [40], or AM [55]. One study compared CAF/CTG with CAF/CTG/PRF [54]. Only one study [41] did not report data on the inclusion of smoking volunteers.

Table 1 Main characteristics of the included studies

Authors (year)	Study design Follow-up	No. of treated recessions (per group) No. of subjects	Age range (mean) Gender	No. of smokers	Miller class	Site of recessions	Surgical technique
CAF vs CAF/PRF							
Aroca et al. (2009)	RCT (parallel) 6 months	67 (C) 67 (T) 20	22–47 (31.7) ♂5/♀15	2	I and II	Maxillary and mandibular	CAF (C) CAF + PRF (T)
Padma et al. (2013)	RCT (split-mouth) 6 months	15 (C) 15 (T) 15	18–35 (NR) NR	0	I and II	Maxillary and mandibular	CAF (C) CAF + PRF (T)
Dogan et al. (2015)	RCT (parallel) 6 months	59 (C) 60 (T) 20	20–45 (37.1) ♂7/♀13	0	I and II	Maxillary	CAF (C) CAF + PRF (T)
Gupta et al. (2015)	RCT (split-mouth) 6 months	15 (C) 15 (T) 26	20–50 (37.2) ♂16/♀10	0	I and II	Maxillary and mandibular	CAF (C) CAF + PRF (T)
Thamaraiselvan et al. (2015)	RCT (parallel) 6 months	10 (C) 10 (T) 20	21–47 (NR) ♂18/♀2	0	I and II	Maxillary and mandibular	CAF (C) CAF + PRF (T)
Dixit et al. (2018)	RCT (parallel) 6 months	12 (C) 12 (T) 12	18–50 (37.5) ♂7/♀5	0	I and II	Maxillary	CAF (C) CAF + PRF (T)
Kuka et al. (2018)	RCT (parallel) 12 months	24 (C) 28 (T) 24	21–41 (32.3) ♂11/♀13	0	I	Maxillary and mandibular	CAF (C) CAF + PRF (T)
CAF/CTG vs CAF/PRF							
Jankovic et al. (2012)	RCT (split-mouth) 6 months	15 (C) 15 (T) 15	19–47 (NR) ♂5/♀10	NR	I and II	Maxillary anterior	CAF + CTG (C) CAF + PRF (T)
Eren and Atilla (2014)	RCT (split-mouth) 6 months	22 (C) 22 (T) 22	18–52 (33.8) ♂9/♀13	0	I and II	Maxillary and mandibular	CAF + CTG (C) CAF + PRF (T)
Tunali et al. (2015)	RCT (parallel) 12 months	22 (C) 22 (T) 10	25–52 (34.2) ♂4/♀6	0	I and II	Maxillary and mandibular	CAF + CTG (C) CAF + PRF (T)
Kumar et al. (2017)	RCT (parallel) 6 months	15 (C) 15 (T1) 15 (T2) 36	NR (33.2) ♂34/♀2	0	I and II	Maxillary	CAF (C) CAF + CTG (T1) CAF + PRF (T2)
Mufti et al. (2017)	RCT (parallel) 6 months	16 (C) 16 (T) 32	NR (36.9) ♂16/♀16	0	I	Maxillary and mandibular	CAF + CTG (C) CAF + PRF (T)
Öncü (2017)	RCT (split-mouth) 6 months	30 (C) 30 (T) 20	20–60 (40) ♂9/♀11	0	I and II	Maxillary and mandibular	CAF + CTG (C) CAF + PRF (T)
Culhaoglu et al. (2018)	RCT (parallel) 6 months	21 (C) 21 (T) 22	21–52 (37.7) ♂10/♀12	0	I	Maxillary and mandibular	CAF + CTG (C) CAF + PRF (T)

Table 1 (continued)

Authors (year)	Study design Follow-up	No. of treated recessions (per group) No. of subjects	Age range (mean) Gender	No. of smokers	Miller class	Site of recessions	Surgical technique
CAF/EMD vs CAF/PRF							
Jankovic et al. (2010)	RCT (split-mouth) 12 months	20 (C) 20 (T) 20	21–48 (NR) ♂8/♀12	0	I and II	Maxillary anterior	CAF + EMD (C) CAF + PRF (T)
CAF/AM vs CAF/PRF							
Agarwal et al. (2016)	RCT (parallel) 6 months	15 (C) 15 (T1) 15 (T2) 30	>18 (NR) ♂22/♀8	0	I and II	Maxillary	CAF (C) CAF + AM (T1) CAF + PRF (T2)
CAF/CTG vs CAF/CTG/PRF							
Keceli et al. (2015)	RCT (parallel) 6 months	20 (C) 20 (T) 40	22–50 (40.7) ♂13/♀27	0	I and II	Maxillary and mandibular	CAF + CTG (C) CAF + CTG + PRF (T)

CCT, controlled clinical trial; *RCT*, randomized clinical trial; *NR*, not reported; *C*, control group; *T*, test group; ♂, male; ♀, female; *CAF*, coronally advanced flap; *PRF*, platelet-rich fibrin; *EMD*, enamel matrix derivative; *CTG*, connective tissue graft; *AM*, amniotic membrane; *RC*, root coverage; *CAL*, clinical attachment level; *KMW*, keratinized mucosa width; *RPM*, rotation per minute; *min*, minute

Relative root coverage

A random effects model was used to evaluate the rRC due to the high heterogeneity that was found ($P < 0.00001$; $I^2 = 91\%$). With respect to the overall effect, use of PRF as adjunct to CAF did not differ significantly ($P = 0.05$) from the use of CAF alone, with a mean difference of 9.60 (95% CI, 0.00 to 19.1) (Table 2, Fig. 1a). When CAF/PRF was compared with CAF/CTG, the fixed effects model was used due to the low heterogeneity observed ($P = 0.40$; $I^2 = 3\%$). There was a statistically significantly greater rRC favoring CAF/CTG, with a mean difference of − 3.97% (95% CI, − 7.76 to − 0.17) (Fig. 1b).

The funnel plot demonstrated an asymmetric distribution, indicating a high risk of publication bias. The asymmetry can be attributed to studies involving the CAF versus CAF/PRF group (Fig. 2a). The sensitivity analysis (exclusion of outliners) suggests that the divergence between the sizes of the sample groups may favor an increased possibility of publication bias. No risk of publication bias was seen for the studies that analyzed CAF vs. CAF/CTG (Fig. 2b).

Clinical attachment level

For CAL, the fixed effects model was used due to the low heterogeneity observed ($P = 0.38$; $I^2 = 7\%$)The use of CAF/PRF improved CAL gain ($P < 0.0001$) compared with the use of CAF alone, with a mean difference of 0.34 (95% CI, 0.18 to 0.51) (Fig. 3a). A random effects model was used to evaluate the CAF/CTG vs. CAF/PRF due to the high heterogeneity that was found ($P = 0.01$; $I^2 = 63\%$). No differences were found ($P = 0.80$) when comparing CAF/PRF vs. CAF/CTG, with a mean difference of 0.05 (95% CI, − 0.34 to 0.43) (Fig. 3b).

Keratinized mucosa width

One study [51] did not report data on KMW. The random effects model was utilized for the evaluation of an increase in KMW due to the high heterogeneity observed ($P = 0.14$; $I^2 = 36\%$). The use of CAF/PRF did not significantly ($P = 0.17$) increase the KMW when compared with CAF alone, with a mean difference of 0.14 (95% CI, − 0.06 to 0.34) (Fig. 4a). However, when CAF/CTG was compared with CAF/PRF ($P = 0.03$), there was a statistically significant improvement favoring the CAF/CTG group, with an MD of − 0.50 (95% CI, − 0.95 to − 0.05) (Fig. 4b).

Probing depth

Two studies [49, 51] did not evaluate PD. The random effects model was used to evaluate PD variation due to the moderate heterogeneity observed ($P = 0.05$; $I^2 = 50\%$). The use of CAF/PRF did not significantly alter PD when compared with CAF

Table 2 Studies comparing CAF vs CAF/PRF, CAF/CTG vs CAF/PRF, CAF/EMD vs CAF/PRF, CAF/AM vs CAF/PRF, and CAF/CTG vs CAF/CTG/PRF

					Methods for PRF preparation		
Authors (year)	Mean difference in RC between baseline and final follow-up (%)	Mean difference in CAL between baseline and final follow-up (mm)	Mean difference in KMW between baseline and final follow-up (mm)	Mean difference in PD between baseline and final follow-up (mm)	Centrifugation system	Volume of blood drawn	Centrifugation parameter speed (RPM) × time (min)
CAF vs CAF/PRF							
Aroca et al. (2009)	91.5 ± 11.4 (C) 80.7 ± 14.7 (T)	2.56 ± 1.56 (C) 2.47 ± 1.85 (T)	− 0.48 ± 1.52 (C) − 0.24 ± 0.77 (T)	0.30 ± 0.69 (C) 0.24 ± 0.77 (T)	EBA20 centrifuge, Hettich, Germany	40 ml	3000 × 10
Padma et al. (2013)	68.4 ± 17.4 (C) 100 ± 0.0 (T)	2.69 ± 0.36 (C) 3.75 ± 1.9 (T)	2.19 ± 1.00 (C) 2.44 ± 0.90 (T)	0.87 ± 0.66 (C) 0.31 ± 0.45 (T)	NR	10 ml	3000 × 10
Dogan et al. (2015)	82.1 ± 17.5 (C) 86.7 ± 15.6 (T)	2.58 ± 0.62 (C) 2.83 ± 0.62 (T)	0.14 ± 0.63 (C) 0.58 ± 0.63 (T)	0.29 ± 0.46 (C) 0.37 ± 0.49 (T)	Medifuge, (Silfradentsr, S. Sofia, Italy)	10 ml	2700 × 2 2400 × 4 2700 × 4 3000 × 3
Gupta et al. (2015)	86.6 ± 23.8 (C) 91.0 ± 19.9 (T)	2.46 ± 1.33 (C) 3.26 ± 0.87 (T)	1.40 ± 0.83 (C) 1.60 ± 0.67 (T)	0.40 ± 0.56 (C) 0.73 ± 0.46 (T)	REMI, Laboratories, India	10 ml	2700 × 12
Thamaraiselvan et al. (2015)	65.0 ± 44.4 (C) 74.1 ± 29.0 (T)	1.80 ± 0.91 (C) 2.50 ± 1.17 (T)	0.40 ± 0.69 (C) 0.40 ± 0.69 (T)	0.30 ± 0.48 (C) 0.40 ± 0.51 (T)	NR	10 ml	3000 × 10
Dixit et al. (2018)	79.5 ± 5 (C) 82.8 ± 5.8 (T)	2.50 ± 1.53 (C) 2.42 ± 1.20 (T)	NR	NR	NR	5 ml	2700 × 12
Kuka et al. (2018)	74.6 ± 8.05 (C) 88.3 ± 15.4 (T)	1.74 ± 0.24 (C) 2.10 ± 0.61 (T)	0.65 ± 0.47 (C) 0.70 ± 0.42 (T)	− 0.78 ± 0.34 (C) − 0.65 ± 0.24 (T)	Hettich EBA 20 (Tutlingen, Germany)	10 ml	3000 × 10
CAF/CTG vs CAF/PRF							
Jankovic et al. (2012)	92.0 ± 15.5 (C) 88.7 ± 10.7 (T)	2.96 ± 0.42 (C) 2.87 ± 0.39 (T)	1.44 ± 0.63 (C) 0.88 ± 0.71 (T)	0.16 ± 0.09 (C) 0.21 ± 0.10 (T)	NR	10 ml	3000 × 10
Eren and Atilla (2014)	94.2 ± 12.1 (C) 92.7 ± 13.7 (T)	2.09 ± 0.98 (C) 2.43 ± 0.89 (T)	1.22 ± 1.87 (C) 0.93 ± 1.87 (T)	− 0.36 ± 0.64 (C) − 0.02 ± 0.43 (T)	NF200 (Nüve Laboratory Equipments, Turkey)	10 ml	400 g × 12 (RPM NR)
Tunali et al. (2015)	77.4 ± 17.4 (C) 76.4 ± 13.2 (T)	3.04 ± 1.69 (C) 2.7 ± 2.17 (T)	0.6 ± 0.90 (C) 0.53 ± 0.89 (T)	0.31 ± 0.64 (C) 0.15 ± 0.68 (T)	Universal 320 table centrifuge (Heittich Instruments)	10 ml	2700 × 12
Kumar et al. (2017)	53.3 ± 40.4 (C) 58.9 ± 25.9 (T1) 74.4 ± 36.7 (T2)	1.00 ± 1.06 (C) 1.20 ± 0.94 (T1) 1.73 ± 0.88 (T2)	1.14 ± 1.31 (C) 1.20 ± 0.56 (T1) 1.14 ± 0.64 (T2)	−0.40 ± 0.29 (C) 0.00 ± 0.00 (T1) 0.34 ± 1.17 (T2)	PC-02 machine (Process Ltd., France)	10 ml	2700 × 12
Mufti et al. (2017)	64.7 ± 37.8 (C) 51.1 ± 36.9 (T)	0.32 ± 1.14 (C) 1.25 ± 1.01 (T)	0.32 ± 0.80 (C) 0.38 ± 1.93 (T)	NR	NR	10 ml	3000 × 10
Öncü (2017)	84 ± 16.3 (C) 77.1 ± 14.2 (T)	3.76 ± 1.44 (C) 3.3 ± 1.59 (T)	1.73 ± 1.17 (C) 1.1 ± 1.16 (T)	0.16 ± 0.76 (C) 0.30 ± 0.63 (T)	PC-02 machine (Process Ltd., France)	9 ml	2700 × 12
Culhaoglu et al. (2018)	80.1 ± 18.9 (C) 69.7 ± 15.3 (T)	2.31 ± 1.07 (C) 1.65 ± 0.97 (T)	2.24 ± 1.33 (C) 0.19 ± 1.61 (T)	0.14 ± 0.34 (C) 0.16 ± 0.38 (T)	PC-02 machine (Process Ltd., France)	10 ml	2700 × 12
CAF/EMD vs CAF/PRF							
Jankovic et al. (2010)	70.5 ± 11.8 (C) 72.1 ± 9.6 (T)	2.65 ± 1.19 (C) 3.27 ± 1.19 (T)	0.60 ± 0.98 (C) 0.17 ± 0.90 (T)	0.1 ± 0.84 (C) 0.22 ± 0.83 (T)	NR	10 ml	3000 × 10
CAF/AM vs CAF/PRF							

Table 2 (continued)

					Methods for PRF preparation		
Authors (year)	Mean difference in RC between baseline and final follow-up (%)	Mean difference in CAL between baseline and final follow-up (mm)	Mean difference in KMW between baseline and final follow-up (mm)	Mean difference in PD between baseline and final follow-up (mm)	Centrifugation system	Volume of blood drawn	Centrifugation parameter speed (RPM) × time (min)
Agarwal et al. (2016)	33 ± 40.4 (C)	0.86 ± 1.70 (C)	0.87 ± 1.32 (C)	0.14 ± 0.96 (C)	REMI laboratories, India	10 ml	2700 × 12
	36 ± 25.9 (T1)	1.20 ± 1.75 (T1)	0.93 ± 1.87 (T1)	0.26 ± 0.43 (T1)			
	56 ± 36.7 (T2)	1.46 ± 2.49 (T2)	1.20 ± 2.00 (T2)	0.00 ± 0.53 (T2)			
CAF/CTG vs CAF/CTG/PRF							
Keceli et al. (2015)	79.9 ± 7.8 (C)	2.50 ± 1.00 (C)	0.78 ± 1.71 (C)	0.0 ± 0.31 (C)	Mikro 22 R centrifuge, Hettich	10 ml	NR
	89.6 ± 2.68 (T)	3.1 ± 0.79 (T)	1.18 ± 1.89 (T)	0.15 ± 0.37 (T)			

CCT, controlled clinical trial; *RCT*, randomized clinical trial; *NR*, not reported; *C*, control group; *T*, test group; ♂, male; ♀, female; *CAF*, coronally advanced flap; *PRF*, platelet-rich fibrin; *EMD*, enamel matrix derivative; *CTG*, connective tissue graft; *AM*, amniotic membrane; *RC*, root coverage; *CAL*, clinical attachment level; *KMW*, keratinized mucosa width; *RPM*, rotation per minute; *min*, minute

alone ($P = 0.60$), with an MD of − 0.04 (95% CI, − 0.19 to 0.11) (Supplemental Fig. 2A). When CAF/PRF was compared with CAF/CTG, the fixed effects model was used due to the low heterogeneity observed ($P = 0.26$; $I^2 = 24\%$). There was no statistically significantly greater PD favoring, with a mean difference of − 0.06% (95% CI, − 0.12 to − 0.01) (Supplemental Fig. 2B).

Assessments of the risk of bias

The results of the risk of bias analyses of the included studies are presented in Supplemental Table 1. None of the studies obtained the highest score in the analysis. Three studies [46, 52, 55] were classified as low risk, while nine [39, 40, 42–45, 47, 50, 54] and five [41, 48, 49, 51, 53] studies were classified as moderate and high risk, respectively.

Discussion

To the best of the authors' knowledge, this is the first systematic review and meta-analysis investigating the use of CAF/PRF for recession coverage in randomized clinical studies compared with all other treatment modalities. The findings from the present systematic review were collected to more specifically address the clinical outcomes and recommendations for PRF with respect to its use in the treatment of Miller class I and II (or Cairo RT 1) gingival recessions compared with the use of other standard modalities currently utilized in the field. Overall, the majority of studies to date compared the use of CAF/PRF vs CAF alone or CAF/CTG (Table 2). Furthermore, additional studies were gathered comparing CAF/EMD vs CAF/PRF, CAF/AM vs CAF/PRF, and CAF/CTG vs CAF/CTG/PRF. Below, we highlight and discuss the summary of evidence from the current categories and further discuss the strengths and limitations of each comparative analysis (Table 3).

CAF alone vs CAF/PRF

In total, 9 studies investigated the use of CAF/PRF vs CAF alone [39, 43, 44, 46, 48, 50, 51, 53, 55]. The meta-analysis demonstrated that the addition of PRF to CAF statistically significantly improved both rRC and CAL gains. No advantage was found between the groups for changes in either PD or KMW. Interestingly, one study demonstrated a statistically significant improvement in rRC in the control group, in which CAF alone was used, compared with the CAF/PRF group [39]. All other studies demonstrated better improvements in root coverage in the CAF/PRF group (Table 2). A study conducted by Padma et al. demonstrated 100% RC following a 6-month healing period with significant improvements in CAL [43]. Interestingly, a number of studies have demonstrated an approximately 10–25% increase in rRC, although not

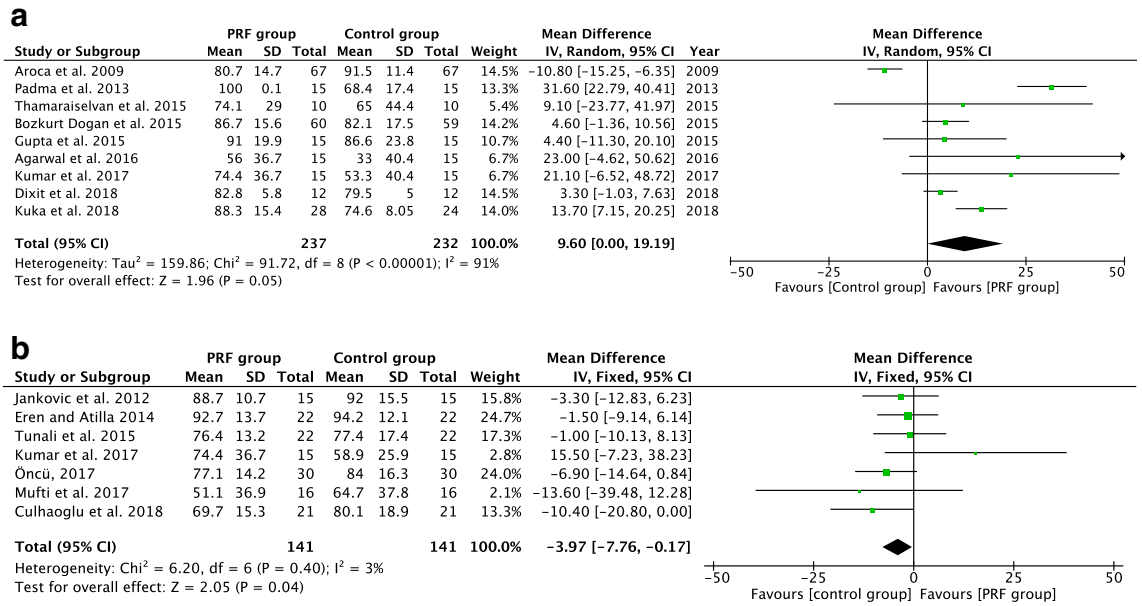

Fig. 1 Forest plot for the event "relative root coverage" (reported as %rRC). **a** Comparison between CAF vs CAF/PRF. **b** Comparison between CAF/CTG and CAF/PRF

statistically significant (Table 2). This lack of significance was most likely due to the low number of included patients, thus validating the need for meta-analysis. In general, the meta-analysis demonstrated an approximately 10–15% higher improvement in terms of rRC when PRF was utilized in combination with CAF compared with the use of CAF alone. Notably, the addition of PRF did not improve KMW.

Reported differences in final outcomes among studies may be due to the investigated parameters. Currently, there are no guidelines with respect to using PRF for treatment of Miller class I and II (or Cairo RT 1) gingival recessions in terms of the ideal thickness of PRF, the number of PRF membranes needed per site, and/or the ideal surgical technique with respect to its use. Interestingly, one study utilized only 5 mL of total blood volume collected yet maintained the use of the standard 2700 RPM for 12-min protocols [51]. Changes in total blood volume utilized during the centrifugation process influence not only the final cell concentration of PRF membranes but also the centrifugation g-forces produced at the actual PRF clot. The final platelet/leukocyte concentration that may have resulted following such modifications remains poorly investigated, which may explain the lack of improvement in rRC in certain

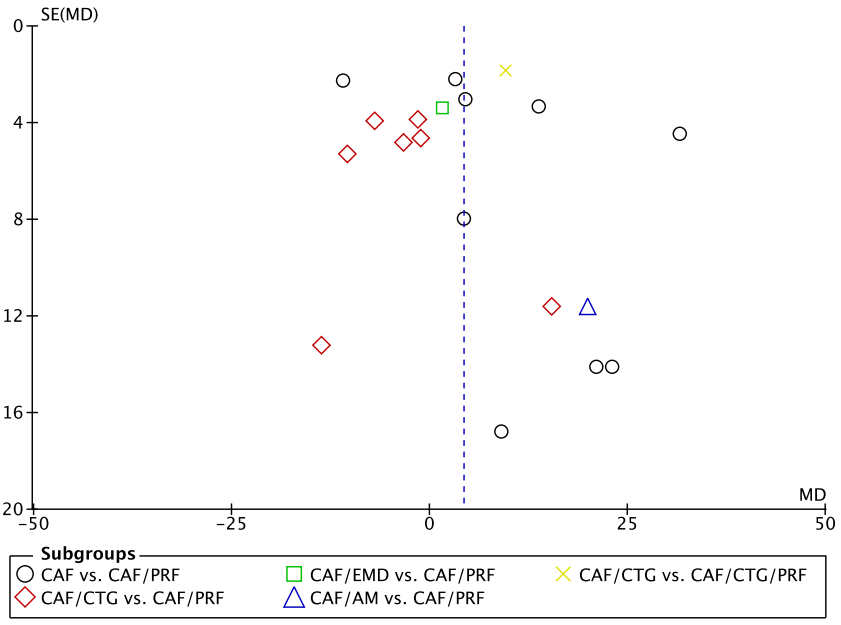

Fig. 2 Funnel plot for the studies reporting the primary outcome "relative root coverage" (reported as %rRC)

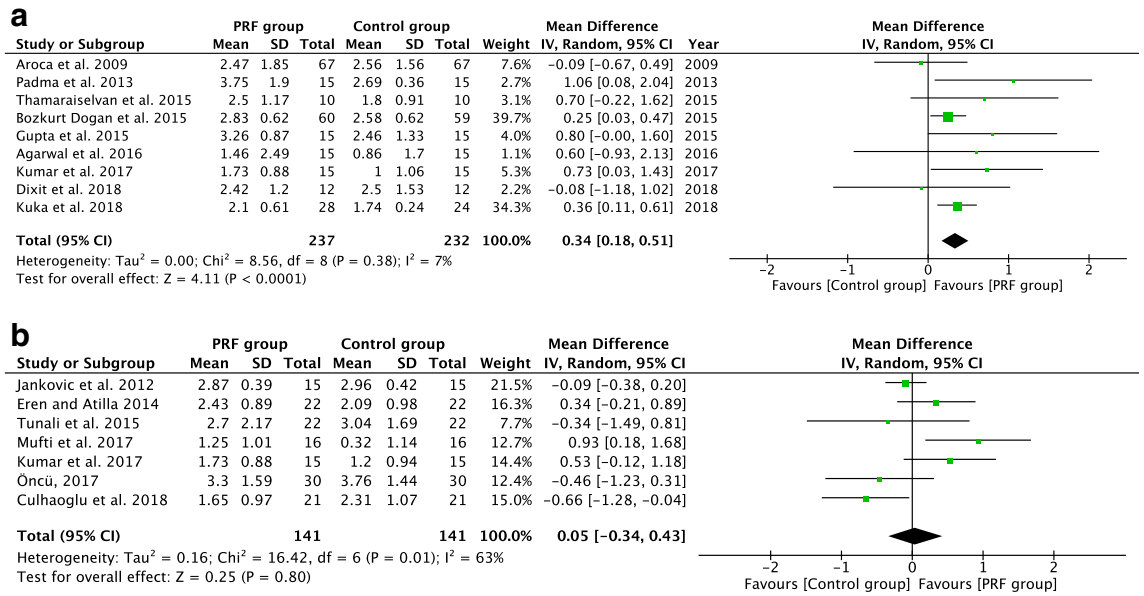

Fig. 3 Forest plot for the event "clinical attachment level" (reported in mm). **a** Comparison between CAF vs CAF/PRF. **b** Comparison between CAF/CTG and CAF/PRF

studies. The proper use of centrifugation protocols and their respective centrifugation tubes is therefore of utmost importance to avoid potential unfavorable results.

CAF/CTG vs CAF/PRF

In total, 7 studies investigated the use of CAF/CTG vs CAF/PRF [41, 42, 45, 47–49, 52]. Findings from the meta-analysis revealed that a statistically significant advantage was observed in the CAF/CTG group for rRC compared with the CAF/PRF group (Table 3). Furthermore, a number of studies concluded that the use of CTG led to statistically significant increases in keratinized tissue thickness compared with the use of PRF. Thus, it may be concluded that compared with the use of PRF, the use of CTG primarily improves the keratinization of tissues, with an increase in both KMW and rRC. Jankovic et al. (2012), Oncu et al. (2017), and Culhaoglu et al. (2018) all demonstrated a statistically significant advantage in KMW in the CAF/CTG group when compared with the CAF/PRF group [47, 52]. In the later study, only a marginal increase in

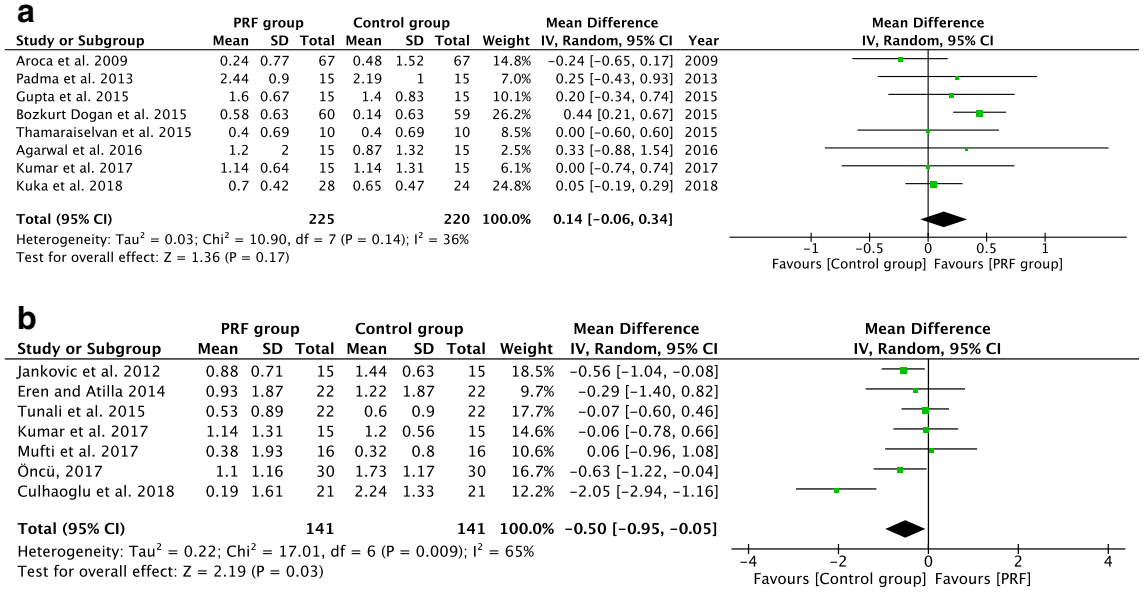

Fig. 4 Forest plot for the event "keratinized mucosa width" (reported in mm). **a** Comparison between CAF vs CAF/PRF. **b** Comparison between CAF/CTG and CAF/PRF

Table 3 Summary of the comparison of 4 outcomes between the platelet rich fibrin (PRF) group and the other treatment modalities. The treatments which led to the statistically better outcomes are shown in the boxes. All empty boxes signify no statistically significant differences between groups. *RC* root coverage, *CAL* clinical attachment level, *KTW* keratinized tissue width, *PD* pocket depth, *CAF* coronally advanced flap, *CTG* connective tissue graft, *EMD* enamel matrix derivative, *AM* amniotic membrane

	RC	CAL	KTW	PD
CAF vs PRF	PRF	PRF		
CTG vs PRF	CTG		CTG	
EMD vs PRF				
AM vs PRF				
CTG vs CTG + PRF	CTG + PRF	CTG + PRF		

KMW was observed in the CAF/PRF group (0.19 mm), whereas the use of CAF/CTG led to a 2.24-mm increase in KMW compared with the findings in controls (over a 10-fold increase). Thus, for the treatment of gingival recessions associated with limited KMW or keratinized tissue thickness, the use of CTG appears to be a better choice than the use of PRF.

CAF/CTG vs CAF/CTG/PRF

Despite the growing use of PRF, only one study has investigated its use in combination with CTG [54]. This therefore presents a limitation, since no meta-analysis was possible. In that study, a statistically significant increase in rRC and CAL was observed, although no change in PD or KMW was observed. Future clinical studies are therefore needed to further investigate whether the addition of PRF to CTG provides additional clinical benefit.

CAF/EMD vs CAF/PRF

Only one randomized clinical study has evaluated the use of CAF in combination with EMD when compared with PRF [40]. Again this is a limitation since a meta-analysis could not be performed. Following a 12-month healing period, no difference was observed in any of the investigated parameters [40].

CAF/AM vs CAF/PRF

One study compared the use of CAF/AM vs that of CAF/PRF [55]. Once again, although a 20% increase in rRC was observed in the CAF/PRF group, the large standard deviation combined with the limited number of clinical studies demonstrated no significant differences in any of the investigated parameters. Future research is needed.

Use of PRF in pain management

One interesting finding reported in several studies was the highlighted decrease in patient morbidity/pain scores associated with the use of PRF. In total, 5 studies have reported advantages in the use of PRF for lowering pain scores compared with the use of CAF alone or CAF/CTG [26, 29, 35, 45, 53]. Furthermore, comparative RCTs utilizing VAS scores have further demonstrated that the use of PRF placed within the donor site of CTG leads to a statistically significant reduction in postoperative pain [56–58]. Therefore, the use of PRF provides an improvement in patient-reported morbidity at the donor site compared with the use of CAF alone, as well as during the harvesting of CTG at the recipient site.

Implications for clinical practice and future direction

A number of important findings were observed within the present systematic review and meta-analysis. In general, the use of PRF in combination with CAF procedures led to statistically significant improvements in rRC and CAL gains compared with the use of CAF alone. Nevertheless, it is important to highlight the fact that relatively no change in KMW or tissue thickness was observed when PRF was utilized, which therefore highlights the fact that PRF alone is not sufficient to improve areas with deficiencies in keratinized tissues.

Conventionally, CTG has been the gold standard in the coverage of gingival recessions. Although several RCTs highlighted within the present systematic review demonstrated comparable results in rRC and CAL, it is important to note that the use of CTG statistically significantly and markedly improved KMW. The meta-analysis therefore confirms the need to utilize CTG for rRC procedures especially in areas of minimal KMW.

Several drawbacks were observed within the present systematic review. First, there exists no long-term data for sites grafted with PRF. Although RCTs on the topic have now been performed for over a decade, no single study has evaluated the long-term follow-up of patients beyond 18 months. This important missing data remains a priority for future research.

Second, very rarely has surgical technique been discussed as a potential means of altering clinical outcomes. As such, variability in the results obtained has been observed, yet little discussion is generally provided by the authors regarding the surgical protocols/guidelines that may further affect surgical outcomes when grafting with PRF. Questions as simple as "How many PRF membranes per tooth should be utilized for recession coverage?" remain vaguely answered, and substantial further research on the topic needed. Similarly, surgical technique has been more recently discussed with respect to whether PRF should be utilized with CAF, tunneling, or vestibular incisions. While each clinical study reports on surgical procedures, studies performed over the upcoming decade

should focus more specifically on necessary technical guidelines while grafting with PRF.

Another highly relevant topic of focus in recent years has been the impact of the centrifugation device and protocol used. Generally speaking, the production of PRF can be achieved with an array of centrifugation devices, although several recent studies have demonstrated various advantages/disadvantages with different systems [59, 60]. This may have caused some of the variability observed in the present systematic review between studies. Recently, Takahashi et al. showed that a fixed-angle centrifuge leads to cell accumulation entirely on the back walls of PRF tubes (distal surface), and membranes are created with an uneven distribution of cells throughout the PRF clot [61]. Furthermore, it was also recently demonstrated that compared with horizontal centrifugation, fixed-angle centrifugation of PRF led to a 4-fold reduction in the ability to concentrate leukocytes within PRF [60]. While little comparative work exists on the topic to date, studies over the upcoming years will ideally further elucidate the role of centrifugation protocols and devices in the final clinical outcomes.

Another interesting topic brought to the forefront of basic research endeavors on PRF has also been the very recent discovery that PRF tube quality is highly variable, with many chemical additives, such as silica and/or silicone, being incorporated within the PRF clots following advanced PRF (A-PRF) protocols [62]. Figure 5 demonstrates the "leftover" silica particles found in a silica-containing tube following A-PRF protocols performed by Tsujino et al. [62]. While little information is available regarding the toxicity effects associated with such additives on the final PRF membrane content, formation, and tissue integration/inflammation, future preclinical research is necessary to further optimize clinical outcomes and patient satisfaction. Recently, Masuki and colleagues demonstrated the acute cytotoxic effects of silica microparticles used for coating of plastic blood-collection tubes on human periosteal cells [64].

Future comparative studies comparing PRF with other commonly utilized biomaterials on the market are needed. For instance, it is surprising that although collagen membranes remain one of the most frequently utilized biomaterials in clinical practice to achieve RC, no single study has compared its clinical outcomes vs those associated with PRF. An array of studies on this topic would better address this missing information over the coming years. It is also more recently common practice to harvest a liquid-injectable PRF that may be utilized to coat collagen membranes [65]. Future research aimed at investigating whether liquid-PRF improves the biocompatibility and/or regenerative potential of collagen membranes is also needed. Future research comparing PRF with other regenerative agents, such as EMD, AM, and rhPDGF, would also be beneficial. Due to the shortage of RCTs on comparative growth factors, no differences have been reported to date among any of the above-mentioned groups. Nevertheless, being entirely autologous, PRF proves to be

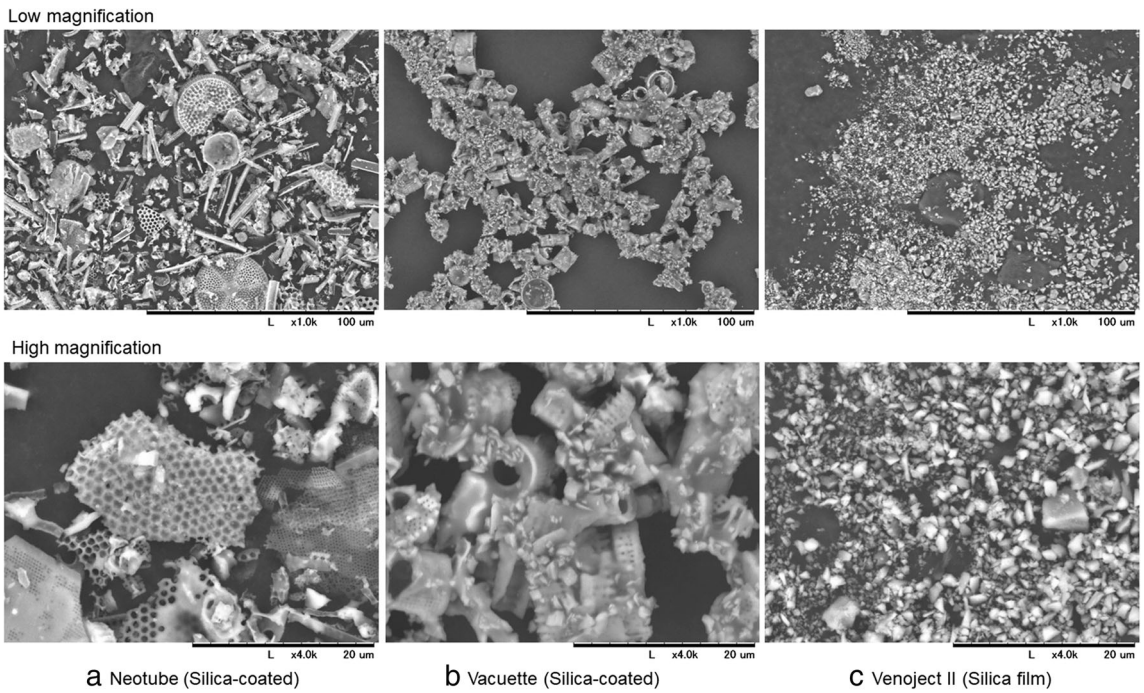

Fig. 5 In this experiment, PRF clots were produced in 3 different commercially available tubes containing silica. Following centrifugation, the clots were removed, the PRF clots were enzymatically digested, and "leftover" remaining silica particles were visually assessed with scanning electron microscopy (SEM). SEM observations of silica microparticles were contained in **a** Neotube tubes, **b** Vacuette tubes, and **c** Venoject II tubes at low (upper) and high magnification (lower). Note the large incorporation of silica microparticles detached from PRF tube walls into PRF clots. Reprinted with permission from Tsujino et al. 2019. [63]

an alternative to commonly utilized synthetic or xenogeneic biomaterials, and additionally favors greater rRC when compared with CAF alone.

Conclusions

The findings from this meta-analysis revealed that compared with the use of CAF alone, the use of CAF/PRF led to statistically significantly higher rRC and CAL, however without substantial changes in KMW. When CAF/CTG was compared with CAF/PRF, no statistically significant difference in terms of PD and CAL was observed between the two approaches. It is however important to note that the CAF/CTG group resulted in significantly better rRC and KMW when compared with CAF/PRF. Therefore, from a clinical perspective in cases with limited or lack of baseline KMW, the use of CTG should be preferred over PRF. No statistically significant differences in any of the investigated parameters were reported among the CAF/EMD, CAF/AM, and CAF/PRF groups. The use of PRF appeared to improve patient-related outcomes such as postsurgical discomfort and pain.

Authors' contributions All authors made substantial contribution to the conception and design of the manuscript. RJM and VM performed the literature search and interpretation of the data. All authors drafted the work and revised it critically for important intellectual content. All authors agree to be accountable for all aspects of the study design and its content. All authors approved the final submitted version.

Compliance with ethical standards

Conflict of interest Richard J Miron holds intellectual property on PRF. All other authors declare no conflict of interest.

Ethical approval No ethical approval was required for this study since it was a systematic review.

Informed consent No informed consent was required.

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