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Influence of alloplastic materials, biologics, and their combinations, along with defect characteristics, on short-term intrabony defect surgical treatment outcomes: a systematic review and network meta-analysis

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Abstract

Background Treating periodontal intrabony defects remains challenging, alloplast materials and biologics are increasingly utilized to improve regeneration outcomes. However, comparative efficacy on alloplast materials remains limited. This study aimed to evaluate the effectiveness of alloplastic materials, both alone and combined with biologics, in treating periodontal defects.

Methods A systematic search of PubMed, Scopus, and CENTRAL identified 74 eligible randomized controlled trials. Meta-analysis assessed data heterogeneity based on defect depth and morphology, classifying defects by wall configuration. Network meta-analysis compared clinical attachment level (CAL) gain, probing depth (PD) reduction, and radiographic linear bone (RLB) gain up to 12 months. Risk of bias was evaluated using the Cochrane Risk of Bias 2 tool, and confidence in network meta-analysis was graded using CINeMA.

Results Defect depth and morphology significantly impacted heterogeneity outcomes at 6 months, but by 12 months, differences across treatments were less significant. Biphasic calcium phosphate (BCP) and nanocrystalline hydroxyapatite (nHA) showed notable improvements in CAL gain, PD reduction, and RLB gain. Combining nHA with platelet-rich fibrin (PRF) outperformed open flap debridement (mean differences at 6 months for CAL gain: 1.37 mm, PD reduction: 1.52 mm and RLB gain: 1.39 mm). SUCRA ranked bioglass and BCP highest for single treatments, while bioglass with platelet-rich plasma and nHA + PRF excelled among combinations.

Conclusions Alloplastic materials, particularly BCP and nHA, significantly enhance periodontal treatment outcomes, especially when combined with biologics like PRF. Defect depth and morphology influence treatment efficacy at 6

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months, though by 12 months, treatment outcomes converge, underscoring the value of early, tailored strategies in periodontal therapy.

Trial registration Not applicable.

Keywords Nanocrystalline hydroxyapatite, Biphasic calcium phosphate, Bioglass, Defect depth, Defect morphology, Biologics, Intrabony defects

Background

Intrabony defects can significantly contribute to periodontal disease progression if left untreated [1, 2]. These defects can lead to the loss of supporting tissues around teeth, increasing the risk of tooth loss over time [1, 2]. The architecture of the defect, particularly its depth, width, and number of remaining bony walls, significantly influences regenerative outcomes [3]. Defects with greater depth, narrower angles, and a higher number of remaining walls have been associated with more favorable clinical attachment level (CAL) and radiographic linear bone (RLB) gain following regeneration [4–8].

Alloplastic materials and biologic agents, such as enamel matrix derivatives (EMD), platelet-rich fibrin (PRF), and platelet-rich plasma (PRP), are utilized either alone or in combination to improve the healing of periodontal defects [9, 10]. Alloplastic materials, including hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), biphasic calcium phosphate (BCP), and bioactive glass (bioglass), are valued for their stability, biocompatibility, wide availability, and effectiveness in promoting bone regeneration [11, 12]. Their versatility allows for customized treatment approaches, making them a valuable option for clinicians aiming to optimize regenerative outcomes. HA closely resembles the inorganic components of bone and teeth but has limitations, such as reduced osteoconductivity and poor degradation, which may hinder its regenerative potential and delay junctional epithelium formation [13–15]. To address these limitations, nanocrystalline hydroxyapatite (nHA) was developed to replicate the natural nanostructure of human tissues, promoting osteoblast colonization, blood vessel growth, and ion homeostasis [16–20]. Clinical and histological studies have validated nHA's effectiveness in treating periodontal intrabony defects [21–24]. β-TCP, which mirrors the calcium-to-phosphate ratio of natural bone, serves as an osteoconductive scaffold that supports both bone formation and periodontal regeneration [25]. It is biocompatible and undergoes rapid resorption, being gradually replaced by natural bone [26, 27]. BCP, a combination of HA and β-TCP in varying ratios, enhances bioabsorbability and accelerates new bone formation by maintaining space and releasing calcium and phosphate ions [26–28]. Animal studies have shown that the HA/β-TCP combination leads to faster bone formation and improved clinical outcomes in both bone and periodontal defects compared to HA [29, 30]. Bioglass, composed of silica, sodium oxide, calcium oxide, and phosphorus pentoxide, directly bonds to bone and soft tissue without forming fibrous layers, promoting bone growth [31, 32]. It has proven effective in the treatment of intrabony defects [33, 34]. Each alloplastic material offers unique physicochemical properties that influence its efficacy in periodontal regeneration. However, its treatment efficacy is generally lower compared to other bone graft materials due to the lack of osteogenic and osteoinductive properties. To improve its regenerative potential, alloplastic materials are often combined with biologics. Biologics, defined as therapeutically active agents used to stimulate regeneration or repair, show promise in enhancing regenerative and reconstructive outcomes. However, the wide variety of biologic agents, each with distinct properties, poses challenges in clinical practice, particularly when determining their optimal use in combination with bone graft materials across different defect architectures.

Understanding the interplay between defect architecture and alloplastic materials, with or without biologics, is crucial for optimizing outcomes in periodontal surgery. This systematic review (SR) and network meta-analysis (NMA) aim to assess the efficacy of various alloplastic materials, including BCP, bioglass, and nHA, both alone and in combination with biologics such as EMD, PRF, and PRP, in treating different types of intrabony defects. The analyses focus on key clinical outcomes, including CAL gain, probing depth (PD) reduction, and RLB gain at 6- and 12-months post-surgery. The findings emphasize how the interaction between alloplastic materials and defect architecture influences treatment outcomes, providing valuable insights for the future design and application of alloplastic materials.

Methods

Study design

This systematic review and network meta-analysis followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), specifically the extension for network meta-analyses [35]. The study protocol was registered with a PROSPERO-registered protocol, registered as number CRD42023381140.

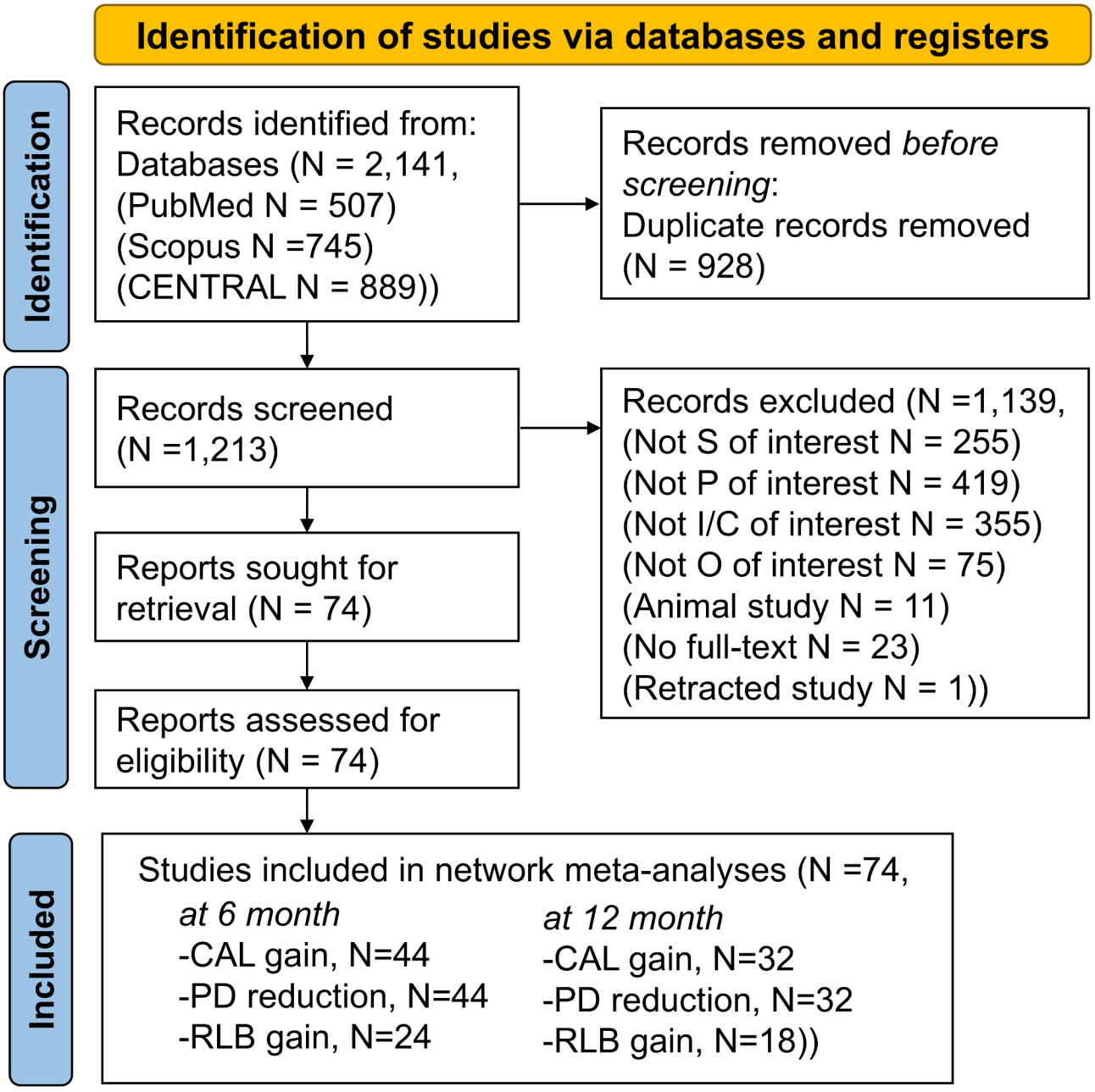

Fig. 1 PRISMA flowchart of study selection

Search strategy and selection criteria

RCTs were identified from PubMed, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) database from inception to September 2024. The details of search terms and strategies for each database were constructed in Supplementary Table S1-S3.

All RCTs were screened by their titles and abstracts, with full-text screening conducted when the information provided was insufficient for selection. No language restrictions were applied. The RCTs were selected by two independent reviewers (KR and SP) based on the following criteria: (1) RCTs of both parallel and split-mouth designs involving periodontitis patients with IBD requiring surgical treatment, (2) studies evaluating the efficacy of alloplastic materials, biologics, and their possible combinations, (3) studies reporting clinical and radiographic outcomes, including CAL gain, PD reduction, and RLB gain at baseline and follow-up periods. RCTs focusing on the treatment of patients with aggressive periodontitis, furcation involvement, dental implants, maxillary sinus augmentation, and alveolar

ridge preservation were excluded. RCTs that combined treatments with guided-tissue regeneration were also excluded.

Data extraction and quality assessment

Data extraction from each RCT was independently carried out by two reviewers (KR and SP) using data extraction forms. General RCT information, such as author names, publication year, study design, and DOI, was recorded. Patient characteristics, including the number of participants, age, gender, smoking status, and systemic diseases, were recorded. Additionally, details about the number of defects, defect depth, and defect type (3-wall, 2-wall, 1-wall, or combinations), were extracted. The radiographic defect depth measured from the alveolar crest to the bottom of the defect at baseline was recorded.

Information on the types of alloplastic materials used and the type of surgery performed (open flap debridement or minimally invasive surgery) was also collected. Outcomes of interest—CAL, PD, and RLB—were documented at baseline and at various follow-up intervals, with means and standard deviations (SD) extracted, as well as mean differences and SD differences. In the analysis of baseline CAL means, only RCTs reporting CAL measurements from the cementoenamel junction (CEJ) to the defect base were included to ensure consistency and facilitate reliable data pooling across studies. The CEJ serves as a fixed anatomical landmark, minimizing variability in measurements and enhancing comparability. Studies using relative attachment level measurements from an acrylic stent were excluded, as variations in stent positioning could affect the accuracy and reliability of pooled data.

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2.0) tool for RCTs [36]. The overall risk of bias was ultimately classified as low, some concerns, or high..

Data synthesis and statistical analysis

Pairwise meta-analysis

All outcomes of interest in this study were continuous data. Unstandardized mean at baseline and mean differences with SD between follow-up and baseline were directly compared and pooled. A fixed or random effect was applied if heterogeneity was absent or present, respectively. Heterogeneity of each outcome was assessed by visual inspection of forest plots, Cochran's Q statistics, and I^2 statistics. A p-value of the Q test less than 0.1 or $I^2 \geq 25\%$ indicated the presence of heterogeneity. Meta-regression analysis with covariables, including risk bias assessment, defect type, surgical type, smoking status, inclusion of patients with systemic diseases, and radiographic bone level at baseline, was conducted to explore the sources of heterogeneity. The regression coefficient or tau [2] was considered to decrease by more than 50% after fitting covariables in the regression model if there was a trend of association.

Network meta-analysis

The treatment efficacies of alloplastic materials, biologics, and their combinations were evaluated using a two-stage network meta-analysis (NMA) approach [37, 38]. In the first stage, direct comparisons were analyzed to estimate pairwise treatment effects. In the second stage, these estimates were integrated with indirect evidence within a network framework, allowing for the comparison of multiple interventions, even without direct head-to-head comparisons. This methodology provided robust and comprehensive estimates of relative treatment effects, enabling the ranking of interventions and offering actionable insights for clinical practice.

The alloplastic materials assessed included biphasic calcium phosphate (BCP), bioglass, and nanohydroxyapatite (nHA), identified through a systematic search. Biologics such as enamel matrix derivative (EMD), platelet-rich fibrin (PRF), and platelet-rich plasma (PRP) were analyzed in combination with these alloplastic materials. Open flap debridement (OFD) was set as the reference in all networks to estimate the relative effectiveness of each intervention. Treatments were coded as follows: 1 = BCP + EMD, 2 = bioglass + EMD, 3 = bioglass + PRF, 4 = bioglass + PRP, 5 = nHA + PRF, 6 = BCP, 7 = bioglass, 8 = nHA, 9 = EMD, 10 = PRF, 11 = PRP, 12 = OFD.

Network maps were generated, featuring nodes and edges, where node size represented the total number of RCTs. In the first stage, regression analysis was performed to obtain beta coefficients and variances for continuous outcomes. In the second stage, these coefficients and variances were pooled using multivariate regression meta-analysis. Inconsistencies were assessed using a design-by-treatment interaction model, with a global test p-value of < 0.05 and a loop-specific approach. Pairwise comparisons were examined through linear combination to identify statistically significant differences.

Clinical and radiographic outcomes were ranked using rankograms and the surface under the cumulative ranking curve (SUCRA). Publication bias was evaluated through adjusted funnel plots and Egger's test, while the confidence rating of the NMA was assessed using the Confidence in Network Meta-Analysis (CINeMA) web tool [37]. Heatmaps were generated using GraphPad Prism version 9.4.1, and all statistical analyses were conducted using STATA software (StataCorp) version 17.0, with a p-value of < 0.05 considered statistically significant.

Results

Study selection and characteristic of included studies

>The PRISMA flow diagram illustrating the electronic search process is presented in Fig. 1. A comprehensive search of the PubMed ($N = 507$), Scopus ($N = 745$), and CENTRAL ($N = 889$) databases identified a total of 2,141 records. After removing 928 duplicates, 1,213 records were screened by title and abstract, resulting in the exclusion of 1,139 records based on predefined inclusion criteria. Full-text assessments were conducted on the remaining 74 articles [16, 21, 34, 38–108]. All included RCTs were published in English. Twelve interventions were identified from the included RCTs: BCP + EMD, bioglass + EMD, bioglass + PRF, bioglass + PRP, nHA + PRF, BCP, bioglass, nHA, EMD, PRF, PRP, and OFD alone. Three biologic treatments, EMD, PRF, and PRP, were included in the analysis as control treatments for their corresponding combination therapies with alloplastic materials. Although RCTs reported outcomes for other alloplastic materials, such as HA, β-TCP with or without biologics, or calcium sulfate, these studies could not form a connected network in the analysis and were not included in the analysis. Adjunctive treatments involving statins, osteoclast-mediated bone resorption inhibitors, or metformin alongside alloplasts or biologics were not included in the analysis [64–66, 72].

The characteristics of the included RCTs are presented in Table 1. Across these RCTs, a total of 2,281 participants and 3,152 defect sites were assessed. Data on CAL gain, PD reduction, and RLB gain between baseline and 6- and 12-month follow-ups were sufficient for pooling. Additional analyses of CAL gain and PD reduction at 3 and 9 months are included in the Supplementary Information. However, the RCTs reporting mean RLB gain at 3 and 9 months did not provide enough data for pooling or forming a connected network (Supplementary Table S4). The number of RCTs reporting treatments for specific defect morphologies for each intervention is summarized in Supplementary Table S5.

Quality of evidence

Of the 74 included RCTs, the within-study bias assessment classified 32 as low risk, 9 as having some concerns, and 33 as high risk (Supplementary Table S6). Three RCTs were deemed high risk due to baseline differences between groups and insufficient details about the randomization process. Seventeen RCTs raised some concerns because of baseline differences in the outcomes of interest between treatments. High risk was attributed to 11 RCTs due to missing data more than 10% of defect sites. Additionally, 28 RCTs were classified as high risk because of missing information on assessor blinding.

Direct meta-analyses

Clinical attachment level (CAL) at baseline and CAL gain at 6- and 12-months post-operative

The mean for CAL at baseline were pooled from 44 RCTs (1,839 defect sites) (Supplementary Table S7). The pooled mean for CAL at baseline was 8.04 mm (95% CI: 7.79 mm, 8.28 mm; $I^2 = 1.25\%$, $p = 0.45$), with no evidence of heterogeneity.

The mean difference (MD) for CAL gain between baseline to 6 months after surgery was estimated from 45 RCTs (1,711 defect sites) (Supplementary Table S9). The pooled MD for CAL gain was 2.59 mm with low heterogeneity (95% CI: 2.34 mm, 2.84 mm, $I^2 = 23.80\%$, $p = 0.03$). Meta-regression and subgroup analysis identified radiographic defect depth at baseline as a key source of heterogeneity for CAL gain ($I^2 = 0.00\%$, $p = 0.94$) at 6 months (Supplementary Figure S1; Supplementary Table S9, S12).

The MD for CAL gain at 12 months compared to baseline was pooled from 32 RCTs (1,403 defect sites) (Supplementary Table S11). The pooled MD for CAL gain at 12 months were 2.77 mm (95% CI: 2.40 mm, 3.13 mm, $I^2 = 51.34\%$, $p < 0.01$). Radiographic defect depth at baseline was identified as the sole source of heterogeneity for CAL gain ($I^2 = 16.05\%$, $p = 0.21$) at 12 months (Supplementary Figure S2; Supplementary Table S11, S12).

Probing depth (PD) at baseline and PD gain at 6- and 12-months post-operative

The mean values for PD at baseline were pooled from 68 RCTs (2,750 defect sites) (Supplementary Table S7). The pooled USM for PD was 7.52 mm (95% CI: 7.36 mm, 7.68 mm; $I^2 = 0.00\%$, $p = 1.00$), with no evidence of heterogeneity.

The MD for PD reduction between baseline to 6 months after surgery was estimated from 44 RCTs (1,739 defect sites) (Supplementary Table S9). The pooled MD for PD reduction was 3.12 mm (95% CI: 2.90 mm, 3.34 mm, $I^2 = 12.83\%$, $p = 0.16$). Meta-regression and subgroup analysis identified radiographic defect depth at baseline as a key source of heterogeneity for PD reduction ($I^2 = 0.00\%$, $p = 0.57$) at 6 months (Supplementary Table S9, S12). Additionally, defect type was identified as another source of heterogeneity for PD reduction ($I^2 = 0.00\%$, $p = 0.56$) at 6 months (Supplementary Table S9, S12).

The MD for PD reduction at 12 months compared to baseline was pooled from 32 RCTs (1,403 defect sites) for PD reduction (Supplementary Table S11). The pooled MD for PD reduction was 3.47 mm (95% CI: 3.16 mm, 3.78, $I^2 = 42.97\%$, $p < 0.01$). No confounding factors contributed to heterogeneity in PD reduction at 12 months (Supplementary Table S11, S12).

Table 1 Characteristics of included studies

Study	Author	RCT design	Test/ Control	Participant	Defect (*n*)	Mean age (year)	Age range	Male (%)	Surgical type	Smoker	Systemic disease	3-wall defect (%)	Radiographic defect depth (categorical)	Radiographic defect depth (mm)
1	Aimetti et al., 2024 [38]	Parallel	EMD	46	23	55.1	NA	52.17	MIS	-	-	NA	4–6 mm	5.90
			OFD		23	56.2			MIS	-	-	NA	4–6 mm	5.70
2	Pal et al., 2022 [39]	Parallel	BCP + EMD	29	20	33.7	≥ 18	55.17	OFD	-	-	NA	< 4 mm	3.73
			BCP		20				OFD	-	-	NA	< 4 mm	3.47
3	Gupta et al., 2022 [40]	Split mouth	BCP	10	10	34	25–55	60	OFD	+	-	NA	NA	NA
			OFD		10				OFD	+	-	NA	NA	NA
4	Bhatnagar et al., 2022 [41]	Split mouth	BCP	15	15	NA	NA	NA	OFD	-	-	NA	NA	NA
			OFD		15				OFD	-	-	NA	NA	NA
5	Abdulrahman et al., 2022 [42]	Parallel	PRF	11	11	35.64	≥ 18	27	OFD	-	-	36.36	> 6 mm	7.91
			OFD	11	11	36.27		9	OFD	-	-	18.18	> 6 mm	7.73
6	Walia et al., 2022 [43]	Split mouth	PRF	15	15	42	30–50	66.67	OFD	-	NA	NA	NA	NA
			OFD		15				OFD	-	NA	NA	NA	NA
7	Mallappa et al., 2022 [44]	Parallel	nHA + PRF	14	14	39.6	30–50	NA	OFD	-	-	100.00	< 4 mm	3.10
			nHA	14	14	40.2			OFD	-	-	100.00	< 4 mm	3.70
8	Cortellini et al., 2022 [45]	Parallel	EMD	15	15	49.9	28–71	53.33	MIS	NA	NA	NA	NA	NA
			OFD	15	15				MIS	NA	NA	NA	NA	NA
9	Cimões et al., 2022 [46]	Split mouth	EMD	13	13	48.3	36–71	53.85	MIS	-	+	NA	NA	NA
			OFD		13				MIS	-	+	NA	NA	NA
10	Anoixiadou et al., 2022 [47]	Parallel	EMD	18	18	49.8	NA	16.67	MIS	-	-	NA	4–6 mm	4.60
			OFD	18	18	54.92		44.44	MIS	-	-	NA	4–6 mm	4.70
11	Pham et al., 2021 [48]	Split mouth	PRF	30	30	47.9	32–60	73.33	OFD	-	-	NA	NA	NA
			OFD		30				OFD	-	-	NA	NA	NA
12	Csifó et al., 2021 [49]	Parallel	PRF	18	15	55.5	NA	50	OFD	-	-	NA	NA	NA
			EMD		15				OFD	-	-	NA	NA	NA
13	Ashraf et al., 2021 [50]	Parallel	nHA	30	15	NA	25–50	33.33	MIS	NA	-	NA	NA	NA
			OFD		15				MIS	NA	-	NA	NA	NA
14	Apatzidou et al., 2021 [51]	Parallel	PRF	10	10	49.9	20–68	50	MIS	+	NA	60.00	4–6 mm	5.60
			OFD	8	8	54.9		25	MIS	+	NA	50.00	4–6 mm	5.80

Table 1 (continued)

Study	Author	RCT design	Test/ Control	Participant	Defect (*n*)	Mean age (year)	Age range	Male (%)	Surgical type	Smoker	Systemic disease	3-wall defect (%)	Radiographic defect depth (categorical)	Radiographic defect depth (mm)
15	Bahammam et al., 2021 [52]	Parallel	nHA + PRF	60	15	37.4	27–41	46.67	OFD	-	-	NA	4–6 mm	4.40
			nHA		15	40.2	27–48	55	OFD	-	-	NA	< 4 mm	3.60
			PRF		15	37.6	27–48	55	OFD	-	-	NA	4–6 mm	4.60
			OFD		15	41.8	36–48	60	OFD	-	-	NA	< 4 mm	3.90
16	Graziani et al., 2020 [53]	Parallel	EMD	19	19	51.47	NA	53	MIS	+	-	NA	NA	NA
			OFD	19	19	58.36		42	MIS	+	-	NA	NA	NA
17	Xu et al., 2019 [54]	Parallel	PRF	58	30	55.2	NA	55.17	OFD	-	-	0.00	NA	NA
			OFD		30				OFD	-	-	0.00	NA	NA
18	Bodhare et al., 2019 [55]	Split mouth	Bioglass + PRF	20	20	35.9	27–45	55	OFD	-	-	NA	4–6 mm	5.85
			Bioglass		20				OFD	-	-	NA	> 6 mm	6.66
19	Ahmad et al., 2019 [56]	Parallel	PRF	16	18	33.06	28–54	37.5	MIS	-	-	100.00	< 4 mm	2.99
			OFD	16	18	37.75	28–55	43.75	MIS	-	-	100.00	< 4 mm	3.15
20	Jalaluddin et al., 2018 [57]	Parallel	PRP	20	10	35	25–45	60	OFD	-	-	NA	< 4 mm	2.90
			BCP		10				OFD	-	-	NA	4–6 mm	4.10
21	Pradeep et al., 2017 [58]	Parallel	PRF	62	29	39.7	NA	54.84	OFD	-	-	NA	4–6 mm	NA
			OFD		29				OFD	-	-	NA	4–6 mm	NA
22	Patel et al., 2017 [59]	Split mouth	PRF	13	13	44	35–55	30.77	OFD	-	-	100.00	NA	NA
			OFD		13				OFD	-	-	100.00	NA	NA
23	Naqvi et al., 2017 [60]	Split mouth	Bioglass + PRF	10	10	NA	20–50	70	OFD	-	-	NA	NA	NA
			Bioglass		10				OFD	-	-	NA	NA	NA
24	Losada et al., 2017 [61]	Parallel	BCP + EMD	21	21	54.9	35–70	71.43	MIS	+	-	0.00	< 4 mm	4.66
			EMD	25	25	50.2		56	MIS	+	-	0.00	4–6 mm	5.20
25	Jalaluddin et al., 2017 [62]	Split mouth	PRP	10	10	NA	25–45	60	OFD	-	-	NA	< 4 mm	2.90
			OFD		10				OFD	-	-	NA	< 4 mm	3.10
26	Chatterjee et al., 2017 [63]	Parallel	PRF	56	28	NA	25–55	NA	OFD	-	-	100.00	NA	NA
			OFD		28				OFD	-	-	100.00	NA	NA
27	Pradeep et al., 2016 [64]	Parallel	PRF	30	30	35	25–45	NA	OFD	-	-	NA	< 4 mm	NA
			OFD	30	30				OFD	-	-	NA	4–6 mm	NA
28	Martande et al., 2016 [65]	Parallel	PRF	48	30	37.6	30–50	50	OFD	-	-	NA	4–6 mm	NA
			OFD		30				OFD	-	-	NA	4–6 mm	NA

Table 1 (continued)

Study	Author	RCT design	Test/ Control	Participant	Defect (*n*)	Mean age (year)	Age range	Male (%)	Surgical type	Smoker	Systemic disease	3-wall defect (%)	Radiographic defect depth (categorical)	Radiographic defect depth (mm)
29	Kanoriya et al., 2016 [66]	Parallel	PRF	30	30	39.6	30–50	50	OFD	-	-	NA	4–6 mm	NA
			OFD	30	30	40.56	30–50	46.67	OFD	-	-	NA	4–6 mm	NA
30	Hoffmann et al., 2016 [67]	Parallel	BCP + EMD	15	15	47.2	18–70	40	OFD	-	NA	0.00	NA	NA
			EMD	15	15	47.5		46.67	OFD	-	NA	0.00	NA	NA
31	Chandradas et al., 2016 [68]	Parallel	PRF	12	12	43.7	NA	NA	OFD	-	-	NA	4–6 mm	NA
			OFD	12	12	470			OFD	-	-	NA	4–6 mm	NA
32	Agarwal et al., 2016 [69]	Split mouth	PRP	10	10	NA	NA	NA	OFD	-	NA	NA	4–6 mm	NA
			OFD	10	10				OFD	-	NA	NA	4–6 mm	NA
33	Kitamura et al., 2016 [70]	Parallel	EMD	112	112	54.8	NA	35.71	OFD	NA	-	35.79	NA	NA
			OFD	43	43	55.2		41.86	OFD	NA	-	43.59	NA	NA
34	Agrali et al., 2016 [71]	Parallel	EMD	6	10	NA	NA	NA	OFD	-	-	0.00	NA	NA
			OFD	6	10				OFD	-	-	0.00	NA	NA
35	Pradeep et al., 2015 [72]	Parallel	PRF	30	30	42.87	30–50	43.33	OFD	-	-	NA	4–6 mm	NA
			OFD	30	30	41.23		53.33	OFD	-	-	NA	4–6 mm	NA
36	Elgendy et al., 2015 [73]	Split mouth	nHA + PRF	20	20	44.25	NA	NA	OFD	-	-	NA	NA	NA
			nHA		20	39.7			OFD	-	-	NA	NA	NA
37	Ajwani et al., 2015 [74]	Split mouth	PRF	20	20	30.5	NA	50	OFD	-	-	NA	< 4 mm	NA
			OFD		20				OFD	-	-	NA	< 4 mm	NA
38	Gupta et al., 2014 [75]	Parallel	EMD	15	22	NA	30–65	50	MIS	-	NA	100.00	4–6 mm	4.73
			PRF	15	22				MIS	-	NA	100.00	4–6 mm	4.89
39	Al Machot et al., 2014 [76]	Parallel	nHA	19	19	50.9	30–65	63.16	MIS	+	NA	0.00	> 6 mm	6.50
			EMD	19	19			42.11	MIS	+	NA	0.00	4–6 mm	5.60
40	De Leonardis et al., 2013 [77]	Split mouth	BCP + EMD	36	34	45.3	30.68	41.67	OFD	-	-	NA	4–6 mm	NA
			EMD		34				OFD	-	-	NA	4–6 mm	NA
			OFD		34				OFD	-	-	NA	4–6 mm	NA
41	Bhutda & Deo, 2013 [78]	Split mouth	EMD	15	15	40.66	37–45	NA	MIS	-	NA	NA	4–6 mm	NA
			OFD		15				MIS	-	NA	NA	4–6 mm	NA

Table 1 (continued)

Study	Author	RCT design	Test/ Control	Participant	Defect (*n*)	Mean age (year)	Age range	Male (%)	Surgical type	Smoker	Systemic disease	3-wall defect (%)	Radiographic defect depth (categorical)	Radiographic defect depth (mm)
42	Pradeep et al., 2012 [79]	Parallel	PRF	54	27	36.8	NA	50	OFD	-	-	NA	4–6 mm	NA
			PRP		27				OFD	-	-	NA	4–6 mm	NA
			OFD		27				OFD	-	-	NA	4–6 mm	NA
43	Pietruska et al., 2012 [80]	Parallel	nHA	15	15	NA	38–55	43.33	OFD	-	-	13.33	4–6 mm	4.30
			OFD	15	15				OFD	-	-	0.00	4–6 mm	4.30
44	Pietruska et al., 2012 [81]	Parallel	BCP + EMD	24	12	NA	34–62	41.67	OFD	-	-	NA	4–6 mm	NA
			EMD		12				OFD	-	-	NA	4–6 mm	NA
45	Thorat et al., 2011 [82]	Parallel	PRF	16	16	31.12	25–47	56.25	OFD	-	-	NA	4–6 mm	NA
			OFD	16	16	30.3	25–45	68.75	OFD	-	-	NA	4–6 mm	NA
46	Subbaiah et al., 2011 [83]	Split mouth	Bioglass	8	8	NA	20–65	NA	OFD	-	NA	NA	NA	NA
			OFD		8				OFD	-	NA	NA	NA	NA
47	Sharma et al., 2011 [84]	Parallel	PRF	42	28	35.34	30–50	42.86	OFD	NA	-	NA	4–6 mm	NA
			OFD		28				OFD	NA	-	NA	4–6 mm	NA
48	Ribeiro et al., 2011 [85]	Parallel	EMD	15	15	48.14	NA	NA	MIS	-	-	NA	4–6 mm	5.24
			OFD	15	15	45.53			MIS	-	-	NA	4–6 mm	5.61
49	Meyle et al., 2011 [86]	Split mouth	BCP + EMD	73	73	46.9	21.1–66.7	31.51	MIS	+	-	0.00	4–6 mm	5.90
			EMD		73				MIS	+	-	0.00	4–6 mm	5.60
50	Kaushick et al., 2011 [87]	Split mouth	BCP + PRP	10	10	NA	20–50	NA	OFD	-	NA	0.00	NA	NA
			BCP		10				OFD	-	NA	0.00	NA	NA
51	Cortellini & Tonetti, 2011 [88]	Parallel	EMD	15	15	48.9	34–59	60	MIS	+	NA	NA	4–6 mm	NA
			OFD	15	15	47.2	34–64	46.67	MIS	+	NA	NA	4–6 mm	NA
52	Kaur et al., 2010 [89]	Split mouth	Bioglass + PRP	10	10	NA	25–45	NA	OFD	-	-	NA	NA	NA
			Bioglass		10				OFD	-	-	NA	NA	NA
53	Heinz et al., 2010 [21]	Split mouth	nHA	15	14	NA	38–52	46.67	MIS	+	-	NA	NA	NA
			OFD		14				MIS	+	-	NA	NA	NA
54	Chambrone et al., 2010 [90]	Split mouth	EMD	10	19	38	28–50	20	OFD	+	-	NA	NA	NA
			OFD		19				OFD	+	-	NA	NA	NA
55	Stein et al., 2009 [91]	Parallel	BCP	30	15	45.4	33–69	31.11	MIS	-	-	NA	4–6 mm	NA
			OFD		15				MIS	-	-	NA	4–6 mm	NA

Table 1 (continued)

Study	Author	RCT design	Test/ Control	Participant	Defect (*n*)	Mean age (year)	Age range	Male (%)	Surgical type	Smoker	Systemic disease	3-wall defect (%)	Radiographic defect depth (categorical)	Radiographic defect depth (mm)
56	Leknes et al., 2009 [92]	Split mouth	EMD	13	13	52.5	41–74	38.46	OFD	+	-	15.38	NA	NA
			Bioglass		13				OFD	+	-	7.69	NA	NA
57	Fickl et al., 2009 [93]	Split mouth	EMD	70	70	46.1	28–63	NA	MIS	NA	NA	NA	NA	NA
			OFD		70				MIS	NA	NA	NA	NA	NA
58	Kasaj et al., 2008 [16]	Parallel	nHA	14	14	52	40–66	50	OFD	NA	NA	14.29	4–6 mm	4.00
			OFD	14	14	53.3			OFD	NA	NA	28.57	< 4 mm	3.60
59	Jepsen et al., 2008 [94]	Parallel	BCP + EMD	38	38	47.5	18–70	76.32	OFD	+	-	0.00	> 6 mm	6.70
			EMD	35	35	46.2		60	OFD	+	-	0.00	> 6 mm	6.90
60	Dybvik et al., 2007 [95]	Parallel	Bioglass	12	12	55.2	35–75	66.67	OFD	+	-	NA	NA	NA
			OFD	7	7	54.7		71.43	OFD	+	-	NA	NA	NA
61	Chambrone et al., 2007 [96]	Split mouth	EMD	13	13	NA	32–43	23.08	OFD	+	-	NA	NA	NA
			OFD		13				OFD	+	-	NA	NA	NA
62	Demir et al., 2007 [97]	Parallel	Bioglass + PRP	15	15	37.87	NA	46.67	OFD	+	-	NA	4–6 mm	NA
			Bioglass	14	14	34.07		42.86	OFD	+	-	NA	> 6 mm	NA
63	Sculean et al., 2007 [98]	Parallel	Bioglass + EMD	25	12	46	38–55	44	OFD	-	-	8.33	NA	NA
			EMD		13				OFD	-	-	7.69	NA	NA
64	Kuru et al., 2006 [99]	Parallel	Bioglass + EMD	23	20	44.7	NA	NA	OFD	NA	NA	NA	> 6 mm	NA
			EMD		20				OFD	NA	NA	NA	> 6 mm	NA
65	Bokan et al., 2006 [100]	Parallel	EMD	19	19	59.7	NA	42.11	MIS	+	-	0.00	NA	NA
			OFD	18	18	55		50	MIS	+	-	0.00	NA	NA
66	Sculean et al., 2005 [101]	Parallel	Bioglass + EMD	30	15	NA	NA	53.33	OFD	-	-	13.33	NA	NA
			EMD		15				OFD	-	-	13.33	NA	NA
67	Rösing et al., 2005 [102]	Split mouth	EMD	16	16	NA	29–54	NA	MIS	+	-	NA	NA	NA
			OFD		16				MIS	+	-	NA	NA	NA
68	Francetti et al., 2004 [103]	Parallel	EMD	24	12	46.5	30–66	45.83	MIS	+	-	NA	4–6 mm	5.93
			OFD		12				MIS	+	-	NA	4–6 mm	4.81
69	Wachtel et al., 2003 [104]	Split mouth	EMD	11	11	48	28–64	27.27	MIS	+	NA	NA	4–6 mm	4.8
			OFD		11				MIS	+	NA	NA	4–6 mm	4.4

Table 1 (continued)

Study	Author	RCT design	Test/ Control	Participant	Defect (*n*)	Mean age (year)	Age range	Male (%)	Surgical type	Smoker	Systemic disease	3-wall defect (%)	Radiographic defect depth (categorical)	Radiographic defect depth (mm)
70	Tonetti et al.,2002 [105]	Parallel	EMD	83	83	48	NA	39.8	MIS	+	NA	NA	NA	NA
			OFD	83	83				MIS	+	NA	NA	NA	NA
71	Park et al., 2001 [106]	Parallel	Bioglass	38	21	43.9	31–67	60.53	OFD	-	-	NA	NA	NA
			OFD		17		28–64		OFD	-	-	NA	NA	NA
72	Okuda et al., 2000 [107]	Split mouth	EMD	16	16	56	NA	50	OFD	-	-	44.44	4–6 mm	4.28
			OFD		16				OFD	-	-	16.67	4–6 mm	4.50
73	Zamet et al., 1997 [34]	Parallel	Bioglass	22	22	39.6	23–55	45.45	OFD	NA	NA	NA	NA	NA
			OFD	22	22				OFD	NA	NA	NA	NA	NA
74	Heijl et al., 1997 [108]	Split mouth	EMD	34	34	48	33–68	NA	MIS	+	NA	NA	> 6 mm	NA
			OFD		34				MIS	+	NA	NA	> 6 mm	NA

NA = No data available

Radiographic linear bone (RLB) at baseline and RLB gain at 6- and 12-months post-operative

The mean for RLB at baseline were pooled from 41 RCTs (1,792 defect sites) (Supplementary Table S7). The pooled USM for RLB at baseline was 4.87 mm (95% CI: 4.66 mm, 5.07 mm, I^2 = 22.03%, p = 0.04). Low heterogeneity was observed for the pooled RLB mean mainly due to variation of radiographic defect depth at baseline (Supplementary Table S7, S12).

The MD for RLB gain between baseline to 6 months after surgery was estimated from 24 RCTs (875 defect sites), respectively (Supplementary Table S9). The pooled MD for RLB gain was 1.73 mm (95% CI: 1.40 mm, 2.05 mm, I^2 = 77.68%, p < 0.01). Meta-regression and subgroup analysis identified radiographic defect depth at baseline as a key source of heterogeneity for RLB gain (I^2 = 20.89%, p = 0.17) at 6 months (Supplementary Figure S5; Supplementary Table S9, S12).

The MD for RLB gain at 12 months compared to baseline was pooled from 18 RCTs (813 defect sites) (Supplementary Table S11). The pooled MD for RLB gain was 2.05 mm (95% CI: 1.62 mm, 2.48 mm, I^2 = 81.27%, p < 0.01). No confounding factors contributed to heterogeneity in RLB gain at 12 months (Supplementary Table S11, S12).

Network meta-analyses

Figure 2 illustrates the network maps for CAL gain, PD reduction, and RLB gain at 6 and 12 months post-periodontal surgery. The NMAs at 6 months included BCP + EMD, bioglass + EMD, bioglass + PRF, bioglass + PRP, nHA + PRF, BCP, bioglass, nHA, EMD, PRF, PRP, and OFD alone. At 12 months, the NMAs involved BCP + EMD, bioglass + EMD, BCP, bioglass, nHA, EMD, PRF, PRP, and OFD alone. No global inconsistency was detected across the entire network using the design-by-treatment interaction model (p > 0.05) (Supplementary Table S13). However, the loop-specific approach identified inconsistencies in the BCP + EMD-BCP-OFD loop for all outcomes at 12 months and the BCP + EMD-EMD-OFD loop for CAL gain at 12 months (Supplementary Table S14). NMAs for CAL gain and PD reduction at 3 and 9 months were also conducted as additional analyses for specific alloplastic and combination treatments (Supplementary Figure S6, S7a, S7c, S8a, S8c S10a, S10c, S11a, S11c, S13a, S13c, S14a, S14c; Supplementary Table S15, S17, S19, S21, S26, S28, S30, S32).

CAL gain at 6- and 12-months post-operative

Heatmaps in Fig. 3b illustrate the relative CAL gain of alloplasts, biologics, and their combinations at 6 months. Single alloplast, such as BCP (MD = 1.99, 95% CI = 1.03 mm, 2.94 mm, p < 0.01), bioglass (MD = 1.13 mm, 95% CI = 0.30 mm, 1.96 mm, p < 0.01) and nHA (MD = 0.91 mm, 95% CI = 0.30 mm, 1.52 mm, p < 0.01) significantly improved CAL gain at 6 months compared to OFD and no significant differences observed among individual alloplast treatment (Supplementary Table S16). The combination of biologics and alloplasts appeared to enhance relative CAL gain

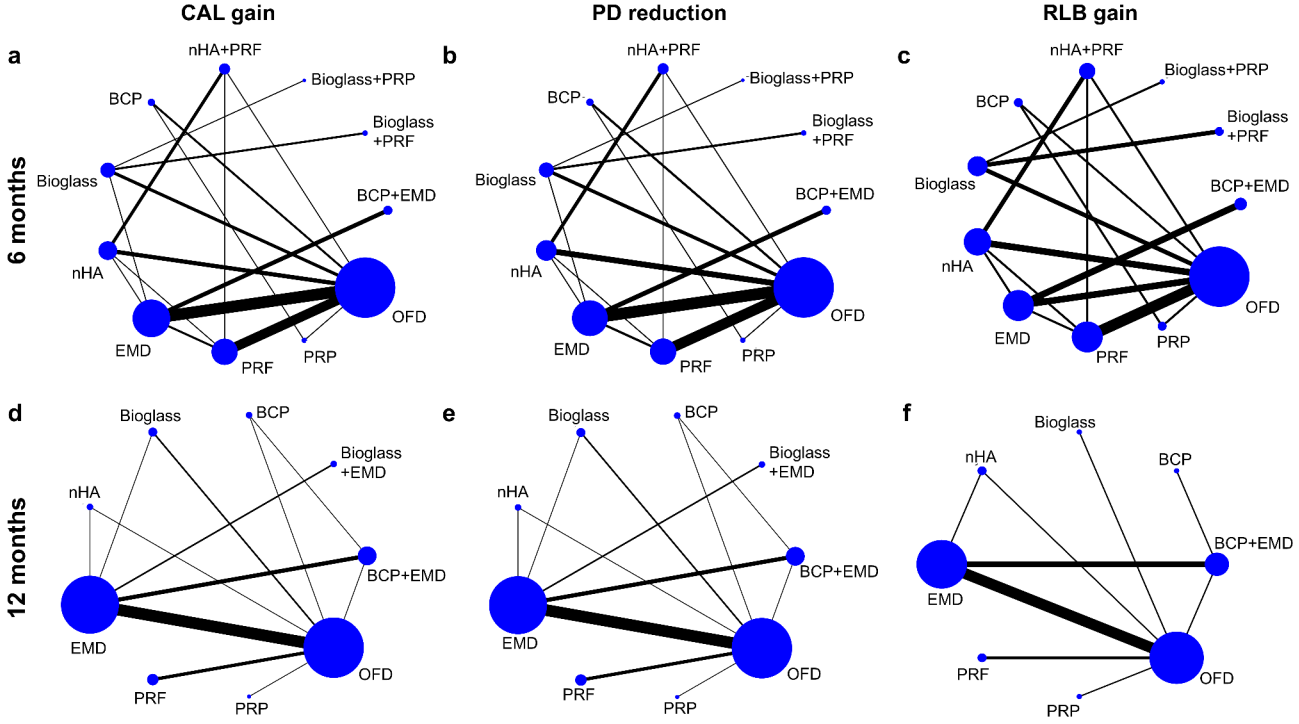

Fig. 2 Network geometry plots for clinical attachment level (CAL) gain, probing depth (PD) reduction and radiographic linear bone (RLB) gain at 6- and 12-months post-surgery. Network comparisons of RCTs for (**a**, **d**) CAL gain, (**b**, **e**) PD reduction, and (**c**, **f**) RLB gain at 6 and 12 months are illustrated. Node size represents the number of RCTs included in each comparison, while line thickness indicates the sample size

compared to single alloplast treatment. Notably, the combination of nHA + PRF significantly increased CAL gain (MD = 1.37 mm, 95% CI = 0.55 mm, 2.19 mm, $p < 0.01$) compared to OFD at 6 months. In contrast, combinations involving BCP and EMD significantly reduced CAL gain compared to other single BCP (MD = -1.66 mm, 95% CI = -2.89 mm, -0.42 mm, $p < 0.01$) at 6 months (Supplementary Table S16). SUCRA ranking and predictive interval plot analysis at 6 months placed bioglass (86%) and BCP (64.6%) among the high-ranked single alloplast treatments, while bioglass + PRP (83.4%) and nHA + PRF (83.5%) ranked highest among combination treatments for CAL gain at 6 months (Supplementary Figure S7b, S10b; Supplementary Table S25).

Heatmaps in Fig. 3e depict the relative CAL gain of alloplasts, biologics, and their combinations at 12 months. There were no significant differences in CAL gain, at 12 months between single alloplast, their combinations, and OFD (Supplementary Table S18). SUCRA ranking and predictive interval plot analyses indicated no difference across treatments for CAL gain at 12 months (Supplementary Figure S7d, S10d; Supplementary Table S25).

PD reduction at 6- and 12-months post-operative

Figure 3c display heatmaps comparing the relative PD reduction achieved by alloplasts, biologics, and their combinations at 6 months. Single alloplasts, such as BCP (MD = 1.69 mm, 95% CI: 0.72 mm, 2.65 mm, $p < 0.01$) and nHA (MD = 0.81 mm, 95% CI: 0.24 mm, 1.39 mm, $p < 0.01$), significantly outperformed OFD in reducing PD at 6 months, with no notable differences among individual alloplast treatments (Supplementary Table S20). However, combinations of BCP and other alloplasts with biologics demonstrated reduced PD reduction compared to single alloplasts or biologics. Notably, the BCP + EMD combination (MD = -1.54 mm, 95% CI: -2.82 mm, -0.26 mm, $p < 0.05$) showed significantly lower PD reduction than single BCP treatment (Supplementary Table S20). SUCRA rankings and predictive interval plot analyses at 6 months placed bioglass (85.7%) and BCP (79.8%) as top-ranked single alloplast treatments for PD reduction, while bioglass + PRP (45.5%) ranked highest among combination treatments. In contrast, BCP + EMD (6.5%) was ranked the lowest for PD reduction across all treatments (Supplementary Figure S8b, S11b; Supplementary Table S25).

Figure 3f present heatmaps illustrating the relative PD reduction achieved by alloplasts, biologics, and their combinations at 12 months. No notable differences in PD reduction were observed at 12 months among single alloplasts, their combinations, and OFD (Supplementary Table S22). Additionally, SUCRA rankings and predictive interval plot analyses showed no significant variations in

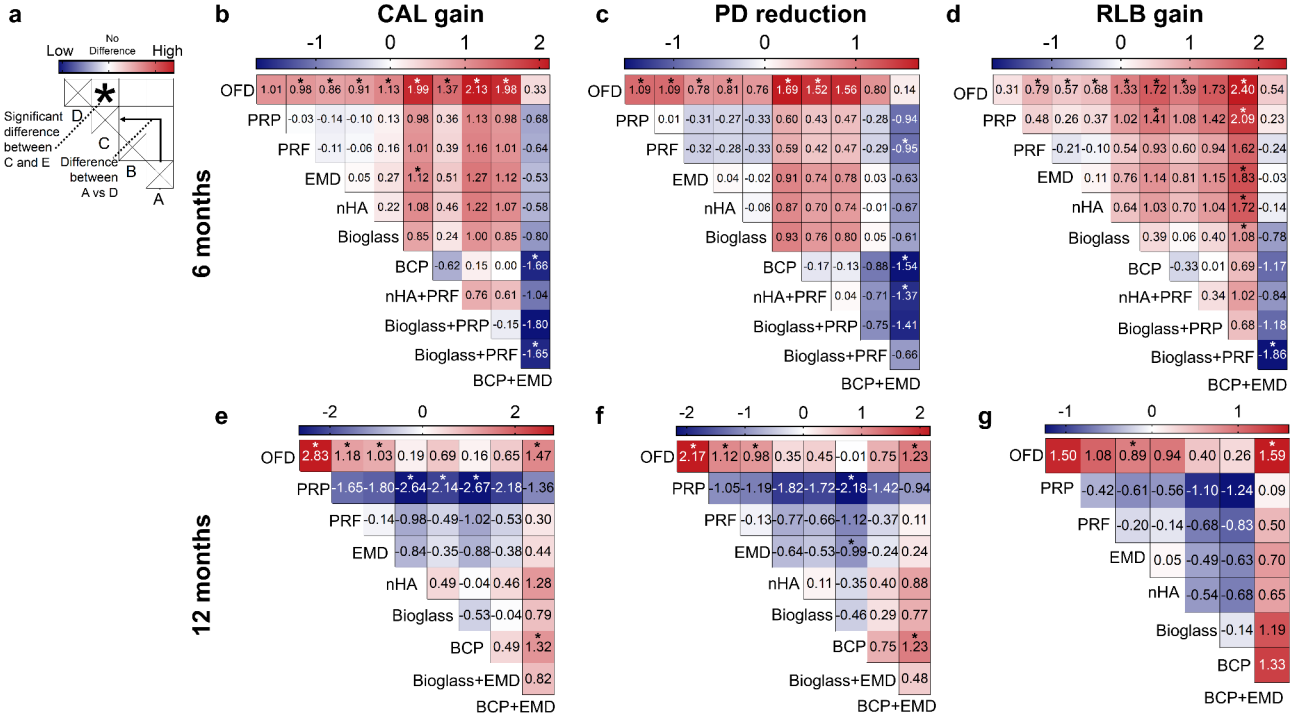

Fig. 3 Heatmaps showing the comparative efficacy of treatments for clinical attachment level (CAL) gain, probing depth (PD) reduction, and radiographic linear bone (RLB) gain at 6- and 12-months post-surgery. Each comparison is read from the lower right to the upper left of the diagonal line, as illustrated in (**a**). Significant differences between treatment pairs are marked with an asterisk. Red represents high differences, blue indicates low differences, and white denotes no significant difference between pairs. (**b**) and (**e**) depict CAL gain at 6 and 12 months. (**c**) and (**f**) show PD reduction at 6 and 12 months. (**d**) and (**g**) illustrate RLB gain at 6 and 12 months. The unit of mean difference is millimeter

PD reduction across treatments at 12 months (Supplementary Figure S8d, S11d; Supplementary Table S25).

RLB gain at 6- and 12-months post-operative

Figure 3d present heatmaps depicting the relative RLB gain achieved by alloplasts, biologics, and their combinations at 6 months. Single alloplasts such as BCP, bioglass, and nHA significantly enhanced RLB gain at 6 months, with no notable differences among these individual treatments (Supplementary Table S23). The nHA + PRF combination demonstrated a significant increase in RLB gain (MD = 1.39 mm, 95% CI: 0.53 mm, 2.25 mm, $p < 0.01$) compared to OFD. Conversely, combinations involving BCP + EMD showed reduced RLB gain compared to single alloplasts and their combinations with biologics. SUCRA rankings and predictive interval plot analyses identified bioglass (79.3%) and BCP (70%) as top-performing single alloplast treatments for RLB gain, while bioglass + PRP (92.8%) and nHA + PRF (73.2%) ranked highest among combination treatments across all outcomes (Supplementary Figure S9a, S12a; Supplementary Table S25).

Figure 3 g display heatmaps illustrating the relative RLB gain achieved by alloplasts, biologics, and their combinations at 12 months. No significant differences in RLB gain were observed at 12 months between single alloplast treatments, their combinations, and OFD (Supplementary Table S24). SUCRA rankings and predictive interval plot analyses also revealed no notable differences across treatments for RLB gain at 12 months (Supplementary Figure S9b, S12b; Supplementary Table S25).

Publication bias assessment

Publication bias for CAL gain, PD reduction, and RLB gain at 3, 6, 9, and 12 months was evaluated using comparison-adjusted funnel plots and Egger's test (Supplementary Figure S13-S15). The analysis revealed evidence of publication bias for CAL gain at 12 months, as well as for PD reduction and RLB gain at both 6 and 12 months.

Assessment of confidence in network meta-analysis

Confidence in the NMAs was assessed using the CINeMA approach (Supplementary Table S27, S29, S31, S33-S35). Indirectness was evaluated based on the presence or absence of patients with smoking and systemic diseases. The results revealed that the confidence level in the NMAs for CAL gain, PD reduction and RLB gain at 6 and 12 months ranged from low to very low. The major factors affecting these confidence levels were a high risk within study and reporting bias.

Discussion

This SR and NMA included data from 74 RCTs to evaluate the effectiveness of various alloplastic materials in treating different patterns of intrabony defects, focusing on CAL gain, PD reduction, and radiographic linear bone RLB gain up to 12 months postoperatively. The NMA approach enables the assessment of relative treatment effects across a network of interventions, overcoming the limitations of lacking direct comparisons. This comprehensive analysis highlighted the benefits of using alloplastic materials, especially during the 6-month follow-up period. Notably, our findings demonstrated that bioglass, BCP, bioglass + PRP, and nHA + PRF were superior to other treatments in promoting periodontal tissue reconstruction.

We assessed the heterogeneity of baseline data for CAL, PD, and RLB by pooling data from multiple RCTs and conducting meta-regression analyses. There was no heterogeneity for baseline CAL and PD means, indicating that follow-up outcomes for CAL gain and PD reduction at 6 and 12 months were comparable across alloplasts, biologics, and their combination treatments. However, low heterogeneity was observed in the baseline RLB, thus RLB gain should be interpreted with caution. Deeper defects were associated with greater RLB gain, aligning with previous findings that highlight the influence of defect morphology on regenerative outcomes [4]. This emphasizes the importance of considering defect characteristics during treatment planning, as deeper defects may experience more pronounced benefits from regenerative approaches.

We further analyzed the association between defect morphology particular the number of defect walls including 1-, 2-, and 3-. Correlations were observed between defect morphology and CAL gain, PD reduction, and RLB gain at 6 months; however, the magnitude and direction of these correlations were ≤ 0.01, indicating minimal clinical significance. Recent consensus reported that the use of biologics combining with biocompatible or biodegradable scaffolds provides added therapeutic benefits in intrabony defects [109]. At 6 months, our results identified radiographic defect depth at baseline as a significant source of heterogeneity across all three outcomes. While radiographic defect depth remained a consistent source of heterogeneity for CAL gain at 12 months, its influence on PD reduction and RLB gain diminished. This suggests that additional factors, beyond initial defect morphology, may play a more prominent role in influencing long-term outcomes. Although narrower defects with more remaining walls are considered more favorable for regenerative outcomes [6, 7], some therapeutic approaches, such as minimally invasive treatments, have demonstrated significant clinical and radiographic improvements in the healing of periodontal intrabony defects, regardless of defect morphology [5].

Our study provides a comprehensive assessment of alloplast efficacy in periodontal regeneration, highlighting both the short-term benefits and the complexities of long-term outcomes. While our analysis spanned various time points, the most pronounced differences in CAL gain, PD reduction, and RLB gain emerged at 6 months post-surgery, underscoring the potent, albeit potentially transient, influence of alloplasts on the initial stages of periodontal healing. Although no statistically significant differences were observed among single alloplast treatments, suggesting comparable efficacy overall, nuanced trends emerged. Both nHA and BCP significantly outperformed OFD across all outcomes at 6 months, with BCP demonstrating superior performance. This suggests that BCP's composition, specifically the synergistic effects of the HA/β-TCP combination, may promote more effective bone regeneration or integration with surrounding tissues, ultimately leading to better clinical outcomes when compared with OFD. This aligns with previous literature indicating that BCP can enhance osteoconductivity and provide a conducive environment for periodontal regeneration [27].

Combining nHA with PRF consistently demonstrated superior outcomes at 6 months compared to single alloplasts and OFD, highlighting the potential synergistic benefits of combining osteoconductive materials with the growth factor-rich PRF to promote enhanced tissue regeneration. However, the lack of long-term data for this combination limits definitive conclusions about its sustained efficacy. In contrast, BCP + EMD demonstrated lower efficacy compared to single BCP and other alloplast-biologic combinations, particularly in non-containable (1-wall, 2-wall and its combinations) defects, a finding consistent with previous RCTs [61, 67, 86]. This raises questions about the suitability of BCP + EMD for specific defect morphologies and underscores the importance of carefully considering both material properties and defect characteristics during treatment planning.

While bioglass, alone or combined with biologics such as PRF or PRP, significantly improved CAL and RLB gain, it demonstrated limited efficacy in reducing PD, even in 3-wall defects. This finding warrants further investigation to understand the underlying mechanisms and explore potential strategies to enhance its effectiveness in addressing probing depths. The combination approaches incorporating bone graft materials with either biologics or barrier membranes have emerged as highly effective treatment modalities for intrabony defects, demonstrating significant probing depth reduction and clinical attachment gain. However, the concurrent use of membranes with biologics is not recommended, as this combination may inhibit the therapeutic benefits

of biologics, particularly their capacity to promote chemotaxis and facilitate the migration of pluripotent mesenchymal cells from soft tissue compartments [109]. Importantly, the cornerstone of successful outcomes remains thorough debridement and precise surgical technique. While the autogenous subepithelial connective tissue graft remains the gold standard for root coverage procedures, the adjunctive use of biologics with alloplastic materials has shown improved initial postoperative healing in root coverage and gingival augmentation therapies [109]. The absence of significant differences among treatments at 12 months, coupled with the lack of long-term data for promising combinations like nHA + PRF, highlights the potential for diminishing returns over time. This highlights the importance of long-term follow-up studies to accurately evaluate the durability of alloplast-mediated regeneration and identify factors that influence long-term stability.

Our findings showed that the differences in CAL gain, PD reduction, and RLB gain were only marginal when comparing grafting to OFD at the 1-year follow-up. One of the limitations in long-term analyses is the limited number of studies reporting long-term outcomes and the inconsistencies in their results. Moreover, when considering the long-term outcomes of periodontal therapy, it is crucial to recognize that numerous factors influence the success of the treatment. These factors could include variations in surgical technique, patient-related factors (e.g., smoking, oral hygiene), or the long-term stability of the regenerative materials. For instance, a previous study found that CAL gain at 12 months was significantly associated with the baseline distance from the cementoenamel junction to the bottom of the defect and the initial radiographic defect angle, but not with the depth of the three-wall subcomponent [8]. This highlights the complex interplay between different aspects of defect morphology and their individual contributions to long-term outcomes.

Limitations

This study has important limitations. First, publication bias was evident across all outcomes, potentially affecting the validity of the results. High heterogeneity in RLB gain at baseline and follow-up also complicates the interpretation of findings. Additionally, inconsistencies in some NMA loops, such as BCP + EMD-BCP-OFD, challenge the conclusions drawn from these comparisons. The limited number of available RCTs investigating alloplast and combination treatments restricts the evaluation of long-term efficacy, especially for nHA + PRF and bioglass + PRP at 12 months. Additionally, investigating the impact of defect morphology on treatment outcomes with various alloplast combinations, along with exploring the cellular and molecular mechanisms behind the differences in alloplast efficacy, are essential next steps. Furthermore, a lack of histological analysis prevents confirmation of regenerative effects at the cellular and tissue levels over longer postoperative periods. Thus, the results should be interpreted with caution, and future research should aim to address these gaps with more comprehensive data and extended follow-up periods.

Conclusion

Within the limitation of this study, it is suggested that among various alloplasts, BCP and nHA, especially when combined with biologics like PRF, may offer additional benefits in managing periodontal defects during the 6-month postoperative period. However, while the short-term outcomes are promising, the differences between treatments become less pronounced at the 12-month mark, indicating that the effect may converge over time. This underscores the importance of longer-term follow-up to thoroughly evaluate the sustained impact of alloplastic materials and their combinations, particularly BCP, nHA, bioglass, nHA + PRF, and bioglass + PRP. Clinicians should consider defect morphology when selecting materials to optimize treatment outcomes, and long-term management strategies are essential to evaluate the enduring efficacy of these interventions.

Abbreviations

SR	Systematic review
MA	Meta-analysis
NMA	Network meta-analysis
RCT	Randomized controlled trial
SUCRA	Surface under the cumulative ranking curve
IBD	Intrabony defects
CAL	Clinical attachment level
PD	Probing depth
RLB	Radiographic linear bone
OFD	Open flap debridement
BCP	Biphasic calcium phosphate
HA	Hydroxyapatite
nHA	Nanocrystalline hydroxyapatite
β-TCP	β-Tricalcium phosphate
bioglass	Bioactive glass
EMD	Enamel matrix derivative
PRF	Platelet-rich fibrin
PRP	Platelet-rich plasma
USM	Unstandardized mean
USMD	Unstandardized mean difference
CI	Confidence interval
PrI	Predictive interval

Supplementary Information

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Supplementary Material 1

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Author contributions
KhR and SP conducted reviews, extracted data, and assessed quality. KhR, SP, KaR, KS, MR, JT, TP performed data analysis and interpreted results. KhR, SP, and KaR drafted the manuscript. All authors critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

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Data availability
All the data produced throughout this systematic and network meta-analysis are incorporated in this published article and Supplementary information.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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