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Stem cell therapies for periodontal tissue regeneration: A meta-analysis of clinical trials

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ABSTRACT

Objective: Stem cell therapy in periodontal tissue regeneration has reported optimistic regenerative results; evidence supporting its superiority over conventional methods is still ambiguous. Therefore, this meta-analysis aims to evaluate the therapeutic effects of stem cells in human periodontal regeneration.

Design: A literature search was conducted to retrieve relevant articles on periodontal regeneration in stem cell therapy. A meta-analysis of the studies was conducted using the Stata software.

Results: Fifteen studies that examined the effect of stem cell therapies on periodontal tissue regeneration in 369 patients were selected from databases. Regardless of the various types of cells, both odontogenic (periodontal ligament, dental pulp, gingiva stem cell) and non-odontogenic (bone marrow, periosteum-derived, and umbilical cord stem cells), the cell therapies witnessed significant improvements in terms of clinical attachment level (SMD, −0.67; 95CI, −0.90 to −0.43), probing depth (SMD, −0.76; 95% CI, −1.21 to - 0.31), radiographic intrabony defect depth (SMD, −0.87; 95% CI, −1.52 to −0.23), and histomorphometric analysis of mineralized bone (SMD, 0.80; 95% CI, 0.42 to 1.19) when compared to traditional without-cell treatment in patients. However, evidence on gingival recession, alveolar thickness gain, bone mineral density of bone core, and bone volume fraction of bone core outcomes did not reach statistical significance.

Conclusions: Evidence suggests that the implementation of stem cell therapies in reconstructing compromised gingiva and alveolar bone tissue produces positive outcomes compared with conventional approaches. However, further well-designed investigations are needed to comprehensively identify the most effective source of cells and biomaterials for each case.

1. Introduction

Periodontal disease (PD) is currently one of the world's most common oral diseases with a global prevalence of up to 50%.[1] PD is a chronic inflammatory condition affecting the periodontium, a structure composed of the gingiva, periodontal ligament, cementum, and alveolar bone.[2] Up to now, a large number of researches[1,3,4] have pointed out the consequences of periodontitis such as the destruction of the soft tissues (e.g. recession of the gingiva, destruction of the periodontal ligament, formation of the periodontal pocket), resorption of the hard tissues (e.g. marginal alveolar bone loss) and eventually tooth loss. These adverse dental complications result in masticatory dysfunction but esthetic appearance is also adversely affected, which later leads to a decrease in quality of life.[1,5]

Since periodontal damage is mostly irreversible, several periodontal regeneration therapies have been proposed to arrest these periodontal lesions and prevent their progression. Initial approaches to achieve the regeneration of the periodontium include conventional surgical procedures, the use of barrier membranes through space maintenance, clot stabilization, and relocation of the periodontal tissue.[6] Recently, minimally invasive surgery – a novel standard for medical procedures - has been applied in periodontal therapy and has already achieved impressive results: less morbidity and better esthetics for the patients.[7] Along with the advancements in biomaterial science and engineering,

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especially in multifunctional scaffolding biomaterials, periodontal regenerative therapy has become very popular and has developed rapidly.[8,9]

One outstanding innovation in tissue regeneration is stem cell-based therapy. By transplanting autogenous or homogenous stem cells cultured outside the patient's body, tissues that have lost their functions can be triggered to regenerate or even replaced by the stem cells themselves.[10] Specifically, in terms of periodontal regeneration, stem cells of both odontogenic (periodontal ligament, dental pulp, deciduous teeth, apical papilla, and dental follicle) and non-odontogenic (bone marrow, adipose tissue, etc.) origins have been proven to possess formidable abilities to reconstruct the damaged periodontium.[10–13] The effects of using dental pulp stem cells (DPSCs), periodontal ligament-derived stem cells (PDLSCs), and mesenchymal stem cells (MSCs) have also been reported in clinical dental practice. Current case series have reported successful clinical and radiographic results using DPSCs in the treatment of bony defects.[14,15–18] A recent systematic review concluded that PDLSCs could facilitate periodontal regeneration more effectively than DPSCs.[19] In the last few years, based on the unlimited self-renewal and differentiation potential of stem cells used in regenerative medicine, mesenchymal stem cell-based (MSCs) tissue engineering has emerged as a novel and promising approach for the periodontal tissue regeneration.[20,21,22] The combination of MSCs, osteogenic factors, and a scaffold (beta-tricalcium phosphate, hydroxyapatite/tricalcium phosphate, etc.) during cell cultivation has also been proven to succeed in recreating an osteogenic construct.[23]

Citterio, Gualini et al. indicated that stem cell therapy provided good regenerative outcomes in treating intrabony defects, including the improvement in clinical attachment level (CAL), probing depth (PD), gingival recession (GR) measurements, and radiographic bone defect fill.[24] Novello et al. recognized better CAL improvement in the MSCs group than in the control group, but no significant difference in PD or GR was observed between the two groups.[25] Another meta-analysis in 2022[26] revealed greater healing in PD, CAL, bone defect depth (BDD), and GR in the group treated with stem cells where the CAL index showed the most improved result and GR showed the least. These included meta-analyses all reported no adverse effects or severe complications, thus acknowledging the safety of this stem cell-based therapy.

Although the outcomes often favor cell-based therapy, more clinical research is required to fully evaluate the promising potential of cell therapy in periodontal regeneration. For a more general and comprehensive assessment of existing information, this meta-analysis was conducted to assess the efficacy of stem cell therapy on clinical, radiographic, computed tomography parameters, and histomorphometry for periodontal tissue reconstruction in humans.

2. Materials and methods

2.1. Study design

Meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The focused question was, "What is the efficacy of stem cell therapies for periodontal tissue regeneration in comparison with conventional without-cell treatment in humans?". Three authors independently reviewed articles for study selection, data extraction, and appraisal of the risk of bias. If there were disagreements among them, the unresolved questions would be settled by an argument among all authors to achieve consensus.

2.2. Search strategy and identification of relevant studies

The studies were searched from scientific electronic databases (PubMed, Embase, Cochrane) through keywords: "alveolar ridge preservation"; "lateral alveolar ridge augmentation"; "sinus augmentation"; "mesenchymal stem cells"; "periodontal regeneration"; "biomaterial"; "bone marrow stem cell"; "dental pulp stem cell"; "periodontal ligament stem cell"; "human umbilical stem cell"; "human gingiva fibroblast associated mesenchymal stem cell".

The research subjects are scientific publications on databases that studied the effect of stem cell therapy on periodontal tissue regeneration by assessing parameters including clinical attachment level, probing depth, gingival recession, alveolar thickness gain, analysis of mineralized bone, bone mineral density and bone volume fraction of bone core and intrabony defect depth.

Titles and abstracts were reviewed to narrow down the number of potential studies that met the aforementioned criteria. Full texts were further investigated to obtain final results. Selected articles provided clinical (clinical attachment level, probing depth, gingival recession) radiographic (alveolar thickness gain), tomographic (analysis of mineralized bone, bone mineral density, the bone volume fraction of bone core and intrabony defect depth), and histological outcomes.

2.3. Inclusion and exclusion criteria

Studies by the following inclusion criteria were selected: randomized controlled trials and controlled trials; choice of participants regardless of age, race, gender, or socio-economic status; patients having periodontal defects without any systemic disease, pregnancy, or smoking habits; studies using different types of stem cell and scaffold; evaluating the association between stem cell therapy and periodontal tissue regeneration; revealing the effect of stem cell therapy on reconstructing bony defects. The exclusion criteria are as follows: Case reports, literature reviews; studies experimenting in vitro or on animal models; papers providing insufficient data; papers that were not written in English.

2.4. Data extraction for analysis

The included publishes are studied to extract key information which is then added to a raw data extraction table. Extracted data comprises characteristics of the study (study design, keyword, follow-up period); characteristics of trial participants (age, number of patients, patient's defect characteristic); type of intervention (stem cell type and origin, defect model, combination with other materials); outcome measures such as clinical attachment level (mm), probing depth (mm), gingival recession (mm), alveolar thickness gain (mm), histomorphometric analysis of mineralized bone (%), bone mineral density (mg/cc) and bone volume fraction (%) of bone core, and intrabony defect depth (mm). Metric values were described as mean and standard deviation. If the outcomes have multiple follow-up time points, they can be sorted into two subgroups according to the follow-up period (under-6 months and over-6 months).

2.5. Statistical analysis

A meta-analysis of the studies was conducted using the Stata SE version 15 software (Stata Corp, College Station, TX, USA). Heterogeneity among studies was evaluated by the heterogeneity index I-squared (I^2). In the absence of or low heterogeneity ($I^2 < 50\%$) among studies, meta-analysis was performed using a fixed-effect model. If significant statistical heterogeneity among studies was observed, a random effect model was utilized. The control and cell therapy groups were compared using the standard mean difference (SMD) and 95% Confidence Intervals (CIs). Publications were assessed for publication bias using Egger's test.

3. Results

3.1. Description of the included studies

Studies were searched in scientific databases using specific key terms. A total of 1179 studies were found, 1075 of which were excluded

because the title and abstract did not meet the inclusion criteria. The remaining 104 full-text articles continued to be assessed. Among these, 89 articles were discarded for reasons such as duplicate content, studies with graphical data only, and some articles that did not provide complete data or had treatment groups only. In the end, 15 studies were included in the meta-analysis. Six out of 15 papers have multiple follow-up appointments which can provide data as an independent study. After a closer review, data from these 15 papers were extracted and classified into 4 different models: 07 studies in the periodontal regeneration (PERIO)[17,27–32]; 06 studies in the lateral and/or vertical ridge augmentation (GBR)[33–38]; 01 study in the alveolar ridge preservation (ARP)[39]; 01 study in the sinus augmentation (SINUS).[40] A detailed process of study searching and screening is shown in Fig. 1.

The characteristics of studies in the present meta-analysis were summarized in Table 1. Fifteen studies were published independently over 16 years from 2005 to 2021 evaluating the association between stem cell therapy and periodontal tissue regeneration in 369 patients with alveolar bone/periodontal defects between 18 and 66 years of age.

The types and sources of stem cells harvested and cultivated were also taken into consideration in this meta-analysis. There was a range of different sources to collect stem cells used in these studies: bone marrow stem cells (BMSCs) are very popular at the moment and 6 papers studied the use of BMSCs extracted from autologous bone marrow aspirate and trabecular bone[28,34,36,37,39,40]; 6 studies utilized odontogenic stem cells including 3 from periodontal ligament,[27,29,31] 2 from dental pulp[17,30] and 1 from gingiva[33]; 2 studies applied stem cells harvested from the human umbilical cord[35,38]; periosteum-derived chondroprogenitor and osteoprogenitor cells were used in 1 publication.[32] Another important factor in these studies was the adjuvant use of biomaterials. Many different types of biomaterial (as well as different product brands) were utilized such as Beta-tricalcium phosphate [β-TCP] scaffold, PLA/PGA bioresorbable membrane, enriched with autologous fibrin/platelet lysate (aFPL) …

3.2. *Effect of stem cell therapies for gingiva tissue regeneration*

The effect of stem cell therapies on gingival tissue regeneration was analyzed, the results are shown in Fig. 2. Data on clinical attachment level extracted from 9 studies and then divided into 2 subgroups - under 6 months and over 6 months is presented in Fig. 2a. There was a slight variation among trials with a heterogeneity figure of 33.8% for the former, 16.8% for the latter, and 23% overall. Therefore, a fixed effects model appropriately compared the results for the effect of cell therapy on the clinical attachment level. Under 6 months studies reported that CAL in the cell therapy group decrease 0.63 more than that in the control groups with 95% CI -0.92 to −0.33. The trend was also observed in the

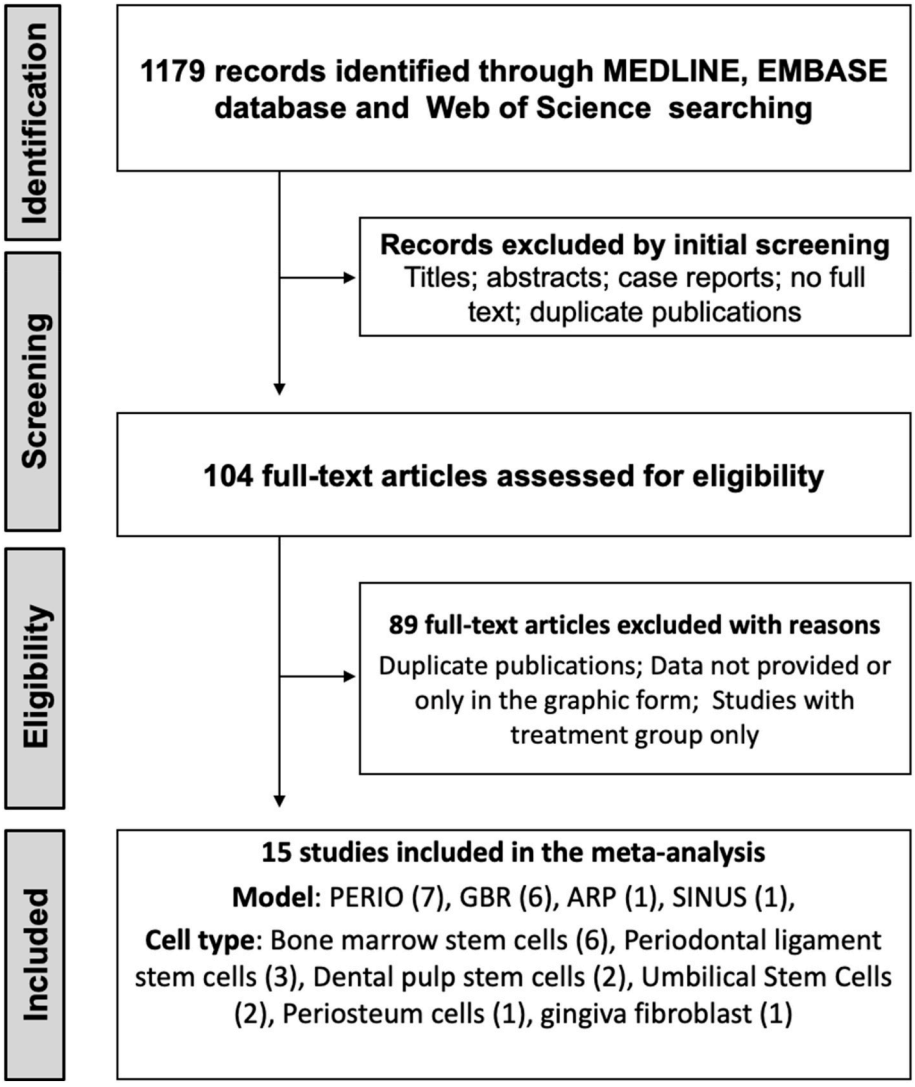


Fig. 1. The selection process of paper for this meta-analysis study. PERIO, periodontal regeneration; GBR, lateral and/or vertical ridge augmentation guided bone regeneration; ARP, alveolar ridge preservation; SINUS, sinus augmentation.

Table 1
Summary of studies included in the meta-analysis.

No.	Study ID	Cell type	Patient type	Group characteristics		Number of Patients			Number of defects			Model	Follow up	Ref.
				C	TR	Total	C	TR	Total	C	TR			
1	[34]	Bone marrow aspirate concentrate	Patients requiring bone augmentation in the anterior maxilla	Allogeneic block grafts	Bone marrow aspirate concentrate + Allogeneic block grafts	10	5	5	40	20	20	GBR	6 months	[34]
2	[37] (1)	Bone marrow aspirate concentrate	Patients lacking four upper incisors needed anterior, maxillary implants.	Xenograft with equino collagen membrane cover	Bone marrow aspirate concentrate + Collagen membrane cover	8	4	4	32	16	16	GBR	4 months	[37]
	[37] (2)												8 months	
3	[36]	Bone marrow aspirate concentrate	Patients requiring a bone graft in the edentulous anterior maxilla	Fresh frozen bone allograft	Bone marrow aspirate concentrate + Fresh frozen bone allograft	10	5	5	40	20	20	GBR	6 months	[36]
4	[39] (1)	Bone marrow stem cells	Patients requiring a tooth extraction	Gelatin sponge	Bone marrow stem cells + Gelatin sponge	12	6	6	12	6	6	ARP	6 weeks	[39]
	[39] (2)												12 weeks	
5	[40]	Bone marrow stem cells	Patients with severe bone atrophy of the upper jaw	β-TCP scaffold	Bone marrow stem cells + β-TCP scaffold	23	12	11	23	12	11	SINUS	4 months	[40]
6	[28] (1)	Bone-Marrow Mesenchymal-Stem Cells	Patients with advanced periodontitis	Collagen scaffolds, enriched with fibrin/platelet lysate	Bone marrow mesenchymal stem cells + collagen scaffolds, fibrin/ platelet lysate	19	10	9	19	10	9	PERIO	6 months	[28]
	[28] (2)												9 months	
	[28] (3)												12 months	
7	[17] (1)	Dental pulp stem cells	Patients with advanced chronic periodontitis	Collagen sponge scaffold	Dental pulp stem cells + Collagen sponge scaffold	29	14	15	29	14	15	PERIO	6 months	[17]
	[17] (2)												12 months	
8	[30]	Dental pulp stem cells	Patients with chronic periodontal disease	Collagen scaffold	Dental pulp stem cells + Collagen scaffold	21	11	10	21	11	10	PERIO	6 months	[30]
9	[32]	Cultured periosteum	Patients with interproximal infrabony osseous defects	PRP and Porous hydroxyapatite granules	Cultured periosteum sheets + PRP and Porous hydroxyapatite granules	30	15	15	30	15	15	PERIO	12 Months	[32]
10	[29] (1)	Periodontal ligament stem cells	Subjects with periodontitis	Bovine-derived bone mineral material	Periodontal ligament stem cell + Bovine-derived bone mineral material	30			41	21	20	PERIO	3 m - Buccal	[29]
	[29] (2)												3 m - Lingual/ Palatal	
11	[27] (1)	Periodontal ligament stem cells	Patients diagnosed with chronic periodontitis	No grafts	Periodontal ligament stem cell grafts	10			20	10	10	PERIO	3 months	[27]
	[27] (2)												6 months	
12	[31]	Periodontal ligament stem cells	Patients with moderate-severe periodontitis	Xenogeneic bone substitute	Periodontal ligament stem cells + Xenogeneic bone substitute	19	10	9	19	10	9	PERIO	12 months	[31]
13	[38]	Umbilical stem cells	Patients with either Miller's class I or II gingival recession	Polylactic acid and polyglycolic acid membrane	Umbilical Stem Cells + Polylactic acid and polyglycolic acid membrane	14	7	7	14	7	7	GBR	6 months	[38]
14	[35]	Umbilical stem cells	Moderate to advanced chronic periodontitis patients	open flap debridement	Umbilical stem cells + Beta tricalcium phosphate + Recombinant human platelet-derived Growth Factor	14			24	12	12	GBR	6 months	[35]

(*continued on next page*)

Table 1 (*continued*)

No.	Study ID	Cell type	Patient type	Group characteristics		Number of Patients			Number of defects			Model	Follow up	Ref.
				C	TR	Total	C	TR	Total	C	TR			
15	[33]	Cultured gingiva fibroblast	Patient with the persistence of the interproximal site	Beta-tricalcium phosphate scaffold and non-perforated membrane	Cultured gingiva fibroblast + Beta-tricalcium phosphate scaffold and non-perforated membrane	20	10	10	20	10	10	GBR	6 months	[33]

Note: C, control; TR, treatment; PERIO, periodontal regeneration; GBR, lateral and/or vertical ridge augmentation guided bone regeneration; ARP, alveolar ridge preservation; SINUS, sinus augmentation.

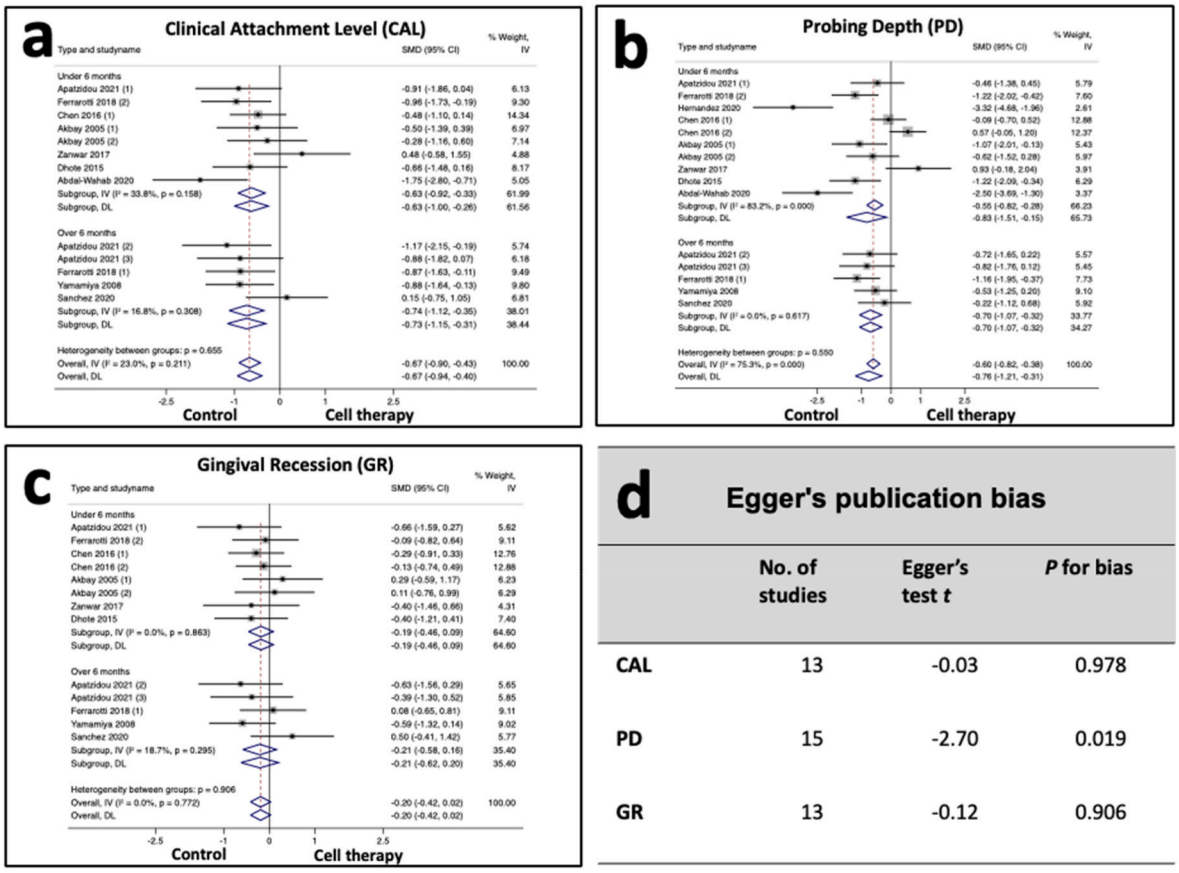


Fig. 2. Evaluation of the effect of stem cell therapies on gingival tissue regeneration by periodontal clinical examination
a-c. Forest plot for the effect of stem cell therapies on gingival tissue regeneration by evaluation of clinical attachment level (CAL), probing depth (PD), and gingival recession (GR); **d.** Egger's publication bias plot shows the publication bias among studies.

over 6-month subgroup with the −0.74 (95% CI, −1.12, −0.35) mean difference between both groups. Overall, it was suggested that cell therapy significantly improved CAL as the CAL mean outcome in the cell therapy group was 0.67 lower than that in the control groups. Egger's test for publication bias was t = −0.03, p = 0.978, indicating no publication bias (Fig. 2d). These results suggest that stem cell therapy helps to significantly decrease the CAL outcome.

The probing depth meta-analysis results from 10 studies assessed as 2 subgroups were presented in Fig. 2b. Overall, there was a decrease in the level of probing depth in the cell therapy group compared to the control group. Studies under 6 months showed a difference of −0.83 (95% CI, −1.51, −0.15) while the SMD value in the over 6 months group was −0.7 (95% CI, −1.07, −0.32). Ultimately, the combined data for both groups was −0.76 (95% CI, −1.21, - 0.31). Egger's test for publication was t = −2.70, p = 0.019, indicating a publication bias (Fig. 2d). This analysis suggests that cell-based therapy significantly improves the condition of periodontal pockets.

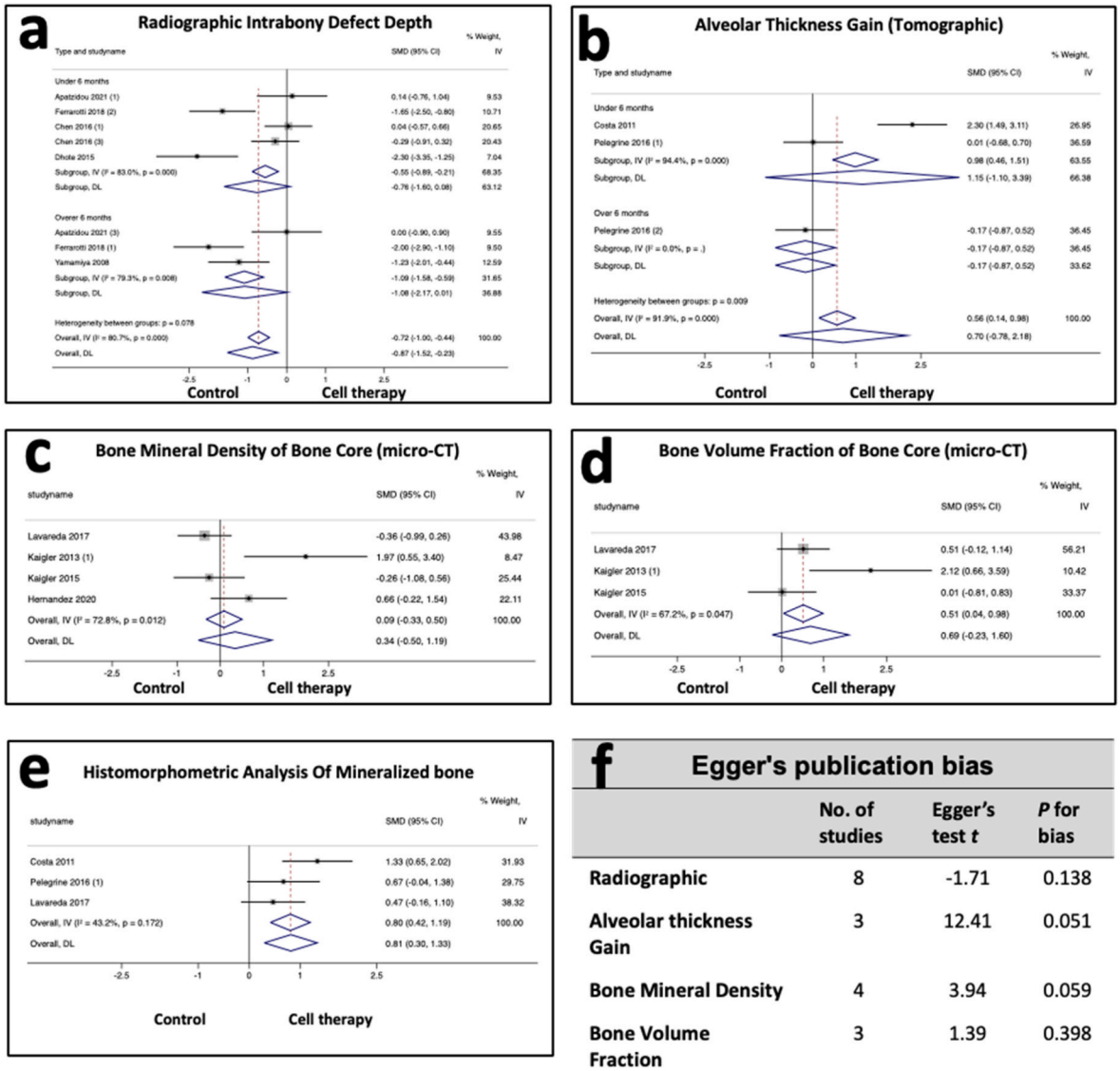
The gingival recession meta-analysis results from 8 studies were presented in Fig. 2c. There was little variation in the data in terms of gingival recession with homogeneity (I^2 = 0%, 18.7%, and 0% in under and over 6 months subgroups, and overall). A fixed-effects model was used to assess the data between the cell therapy and the control group where the standard mean difference SMD was −0.19 (95% CI, −0.46, 0.09) in under 6 months follow-up, −0.21 (95% CI, −0.58, 0.16) in over 6 months follow-up, and −0.20 (95% CI, −0.42, 0.02) in combination. Egger's test for publication was t = −0.12, p = 0.906, indicating no publication bias (Fig. 2d). This proposes that stem cell engineering has a trend in reducing gingival recession in comparison with conventional methods.

3.3. Effect of stem cell therapies for alveolar bone tissue regeneration

The meta-analysis of the effect of stem cell therapies on alveolar bone tissue regeneration through radiographic and computed tomography parameters is shown in Fig. 3a–d. The radiographic intrabony defect depth meta-analysis results from 5 studies divided into 2 subgroups were presented in Fig. 3a. Significant variation with $I^2 = 83.0\%$, 79.3%, and 80.7% for under 6 months, over 6 months, and overall respectively, led to the assessment based on a random-effects model. The standard means difference between the cell therapy and control groups was −0.76 (95% CI, −1.60, 0.08) in the under-6-month subgroup, −1.08 (95% CI, −2.17, 0.01) in over-6-month subgroup and −0.87 (95% CI, −1.52, −0.23) in the overall subgroup. Egger's test for publication bias was t = −1.71, p = 0.138, indicating no publication bias (Fig. 3f). These radiographic data imply that the depth of intrabony defect could be significantly reduced with the use of stem cells.

Tomographic data on alveolar thickness gain assessed as 2 subgroups (under and over 6 months) is shown in Fig. 3b. The data of alveolar thickness gain displayed significant variation in under 6 months and overall group with $I^2 = 94.4\%$ and 91.9% respectively. The mean difference between the 2 groups in under 6 months was 1.15 (95% CI, −1.10, 3.39). In over 6 months of the follow-up group, no variation was witnessed with $I^2 = 0\%$ and the SMD was −0.17 (95% CI, −0.87, 0.52). In the general combined estimate observed, the SMD value was 0.70 (95% CI, −0.78, 2.18). Egger's test for publication was t = 12.41, p = 0.051, indicating no publication bias (Fig. 3f).

The bone mineral density of bone core meta-analysis results from 4 studies with under 6 months of follow-up are presented in Fig. 3c. There was a significant variation in search results with the heterogeneity evaluation of $I^2 = 72.8\%$. A random-effects model revealed a 0.34



f Egger's publication bias

	No. of studies	Egger's test *t*	*P* for bias
Radiographic	8	-1.71	0.138
Alveolar thickness Gain	3	12.41	0.051
Bone Mineral Density	4	3.94	0.059
Bone Volume Fraction	3	1.39	0.398
Histomorphometric Analysis	3	0.55	0.681

Fig. 3. Evaluation of the effect of stem cell therapies on alveolar bone tissue regeneration by imaging examination and histological examination
a-d. Forest plot for the effect of stem cell therapies on alveolar bone tissue regeneration by evaluation of radiographic intrabony defect depth, alveolar thickness gain (Tomographic), the bone mineral density of bone core (micro-CT), the bone volume fraction of bone core (micro-CT). **e.** Forest plot for the effect of stem cell therapies on alveolar bone tissue regeneration by evaluation of histomorphometric analysis of mineralized bone. **f.** Egger's publication bias plot shows the publication bias among studies.

difference (95% CI, −0.50, 1.19) between the test and control groups. Egger's test for publication was t = 3.93, p = 0.059, indicating no publication bias (Fig. 3f).

The bone volume fraction of bone core data was extracted from 3 studies with under 6 months of follow-up included in this meta-analysis (Fig. 3d). Due to the considerable variation (heterogeneity evaluation of $I^2 = 67.2\%$), a random-effects model was used for analysis. The standard mean difference between the cell therapy and control groups was 0.69 (95% CI, −0.23, 1.60). Egger's test for publication bias was t = 1.39, p = 0.398, indicating no publication bias.

The meta-analysis of the effect of stem cell therapies on alveolar bone tissue regeneration through histological analysis was shown in Fig. 3e. Data on histomorphometric analysis of mineralized bone was extracted from 3 studies. $I^2 = 43.2\%$ showed a substantial variation in the data, therefore, a fix-effects model was considered in this assessment. The SMD between the two groups was 0.80 (95% CI, 0.42, 1.19). Egger's test for publication was t = 0.55, p = 0.681, indicating no publication bias. These results suggest that adding stem cells contributes to a significant mineralized bone formation evaluated in histomorphometry when compared to the control group.

4. Discussion

Periodontal lesions start with dental biofilm accumulation, resulting in a cascade of degenerative changes in periodontal tissues[41] which are irreversible since they have little reparative capability and cannot be regenerated.[3] These damaging changes ultimately result in the loss of support for the teeth, which causes them to loosen and fall out over time. Periodontal patients also suffer from masticatory dysfunction, facial deformity, and other problems that detrimentally affect their quality of life, esthetic appearance, and even systemic health.[1] While the gingival recession is a common index for clinical assessment of loss of support within the periodontium, alveolar bone loss is a useful sign of the radiographic evaluation.[4] According to Siow et al.,[42] patients with stage IV periodontitis are still very vulnerable to tooth loss and periodontal progression even with active periodontal therapy.

The important objectives of periodontal therapy are to control and stop the disease progression; eliminate all harmful agents; restore the structure and function of the periodontium and preserve natural teeth. To achieve these goals, the treatment focuses on reducing or eradicating periodontal pockets.[24] Currently, various research has indicated the tremendous potential of periodontal tissue regeneration to improve the periodontal healthcare.[8,9,43] However, these conventional methods result in a considerably increased tissue morbidity, which gives rise to minimally invasive surgery or nonsurgical therapies such as full- and partial-mouth scaling and root planning.[7,44] Thanks to the constant advance of regenerative medicine, more and more novel biomaterials and stem cell therapies have been introduced and therefore there is a need for investigation to validate their efficiency as well as to compare and identify the most suitable for each case.

Bone regeneration has become a popular procedure in reconstructing bony defects due to periodontal complications or the need for sinus floor elevation for better implant placement. Autogenous bone grafts in cases where the bone defect is large and requires sinus lift to achieve appropriate bone volume are regarded as the gold standard.[34,36] However, the harvest of these autogenous bone grafts is highly invasive and has a frequent postoperative morbidity rate at donor sites.[34,45] Recently, bone marrow aspirate concentrate (BMACs), in combination with other biomaterials, has emerged as an attractive alternative to achieve better bone regeneration. In comparison to bone harvesting, the aspiration of autogenous bone marrow is a minimally invasive puncture, causing less discomfort to patients[46] and less risk of complications related to aspiration.[37] Moreover, mesenchymal stem cells contained in bone marrow can tolerate low oxygen concentrations and have the potential for osteogenic, chondrogenic, and adipogenic differentiation, depending on the external stimulus by cytokines.[46] The superior outcomes in new bone formation and post-operative safety have pointed out the great potential of stem cell therapy in reconstructing bony defects as an effective alternative to traditional treatments.[34,36,37,47–49] The application combination of bone marrow stem cells and another biomaterial accompanying bone grafts significantly improved new bone formation in clinical, radiographic, and histological results.[39,45,46,48,50–54] These favorable outcomes suggest that bone marrow stem cell therapy has much potential for safe and effective regeneration of periodontal defects compared to conventional therapeutic strategies.

Stem cells have recently been proven to have regenerative properties that outperform those of regular cell therapies.[11,13] Especially for the regeneration of periodontal tissues, among many different types of stem cell, mesenchymal stem cells (MSCs) are often utilized because of their multi-differentiation potential. Stem cells of both odontogenic (periodontal ligament, dental pulp, deciduous teeth, apical papilla, and dental follicle) and non-odontogenic (bone marrow, adipose tissue, etc.)[10,12] origins are becoming extremely popular in tissue engineering and regenerative medicine.[20] The use of these promising cells has achieved therapeutic efficacy through an array of research[13,21,55,22;,.56–58]

Despite controversy concerning which specific tissues are most likely to provide an appropriate source for cell isolation, cells derived from periodontal ligament tissue have been proven to be capable of forming a complete periodontal attachment apparatus.[29] Periodontal ligament-derived stem cells (PDLSCs) provide excellent effects in the reconstruction of damaged periodontium due to the easy cell isolation,[59] the capacity of maintaining homeostasis, significant regenerative and multi-differentiation potential.[19] Cultured PDLSCs can transform into many different cell types, including cementoblasts, osteoblasts, adipocytes, fibroblasts, and cementum/periodontal ligament (PDL)-like structures.[19] Various controlled clinical trials have indicated the safety and effectiveness of PDLSC-based therapy with no adverse effects and safety problems; reduction of probing depth, gain in clinical attachment, and increase of radiographic bone height.[29,31,59,60]

Dental pulp stem cells (DPSCs), the first dental MSC to be isolated and characterized,[16,19] have also been proven to be effective in periodontal cell therapy. Several in vitro and in vivo experiments have been conducted to prove the strong differentiation potential of DPSCs.[14–17] Besides the evident capacity like any other sources of stem cells, DPSCs are becoming more promising and widely used for regenerative purposes because they share the same origin and similar antigenic pattern of periodontal stem cells and can differentiate in the same lineages[17] including dental pulp–like structures, osteoblasts, and endotheliocytes.[15] DPSCs also possess great advantages for research and cultural process, which are long lifespan, safe cryopreservation, good ability to interact with biomaterials,[15] easy accessibility, and limited morbidity.[16] In addition to autologous DPSCs harvested from patients' malpositioned and compromised third molar, Li's work in 2016 showed that mesenchymal stem cells with retained potential found in the inflammatory dental pulp tissues would be an available resource in the periodontal tissue regeneration.[18]

Nevertheless, we could not neglect the fact that cell therapy also has a few shortcomings when compared with other methods. There are reports of efficacy reduction of regenerative characteristics including shortened lifespan and rapidly diffused extracellular vesicles from MSCs after administration, the need for cautious quality control in large-scale production, the risk of dedifferentiation during amplification, and the most controversial limitation being the highly invasive method of harvesting stem cells.[12,58] There have been solutions to these problems such as the use of stem cells in combination with a supporting scaffold[23]; however, further investigation is still needed to conclude whether stem cell-based therapies are superior to other existing methods.

In conclusion, this meta-analysis indicates that the implementation of stem cell therapies in periodontal regeneration has resulted in improved outcomes compared to conventional methods. Moreover, the addition of biomaterials in combination with diverse types of stem cells has also led to a beneficial influence on the results. Future investigations

on long-term efficiency, and cost-effectiveness along with the types of stem cells and biomaterial used for each case are necessary to determine the superiority of stem cell therapy over traditional approaches.

Author contributions

Conceptualization, T.N.T., and T.D.N.T.; methodology, T.D.N.T., B.H.N.H., T.T.V.H., and T.N.T.; investigation, T.D.N.T., B.H.N.H., T.T.V.H., and T.N.T.; data curation, T.N.T., and T.D.N.T.; writing original draft preparation, T.D.N.T., B.H.N.H., T.T.V.H., and T.N.T.; writing review and editing, T.N.T., and T.D.N.T.; funding acquisition, T.N.T., and T.D.N.T. All authors have read and agreed to the published version of the manuscript.

Data availability

The data underlying the results presented in the study are included in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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