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Evaluate Enhanced Bone Regeneration by Human Adult Dental Pulp Stem Cells Combination with Scaffold: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: The present study has tried to provide evidence in this field by summarizing the results of animal studies because comprehensive results can lead to the decision of clinical trials in this field. Therefore, the present study was conducted to evaluate enhanced bone regeneration by human adult dental pulp stem cells combined with scaffold.

Material and methods: The present study was conducted based on PRISMA 2020-27-item checklist by giving the keywords stem cells, scaffold, bone regeneration and human dental pulp stem cells, all articles available in the international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases and Google Scholar search engine were reviewed until November 2023. STATA/MP. v17 software was used in this meta-analysis. Meta-analysis was performed using mean differences with 95% confidence interval in meta-analysis.

Results: According to meta-analysis, the mean difference in bone regeneration between the experimental and control groups was 1.69 (MD:1.69; 95% CI 1.00 – 2.39, P<0.001). According to meta-analysis, a statistically significant difference was observed considering different groups of scaffolds on bone regeneration in combination with DPSC/SHED (MD:4.84; 95% CI 4.72– 4.95, P<0.001).

Conclusions: The present meta-analysis showed that dental pulp stem cells, along with scaffold, can increase new bone formation and accelerate bone formation compared to the control group.

1. Introduction

One of the main and important challenges for orthopedic and craniofacial surgeons is the functional improvement of bone and complete reconstruction. Several complications have been reported for orthopedic and dental, the most important of which is the repair of traumatic and congenital defects and bone grafting.[1] Various methods have been reported for bone regeneration, including guided bone regeneration and bone grafting.[2] Since autogenous bone grafts are the best choice for bone regeneration, limited access to bone volume and donor site morbidity are reported complications.[3] Studies have used synthetic biomaterials and xenografts for bone graft scaffolds.[4] With the advancement of science and the development of tissue engineering, mesenchymal stem cells (MSCs) have been proposed, which can increase the regeneration of bone tissue.[5, 6] MSCs have been considered suitable because of their self-renewal ability and multilineage differentiation.[7] MSCs can multiply at a high speed, have favorable paracrine, excellent bone-forming potential, and immunomodulatory properties like adult dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED).[8] About twenty years ago, DPSCs were introduced, and MSCs have shown good properties. DPSCs are among MSCs and can exogenously replace osteoblasts and multilineage differentiation. Some studies have shown that hDPSC and SHED induce bone regeneration equally.[9] The scaffold allows regeneration and facilitates growth factor binding. Based on the results of the studies, factors such as the type of stem cells and how they are combined with

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scaffold materials are effective in the success rate of bone regeneration. In this field, studies have been conducted that have been able to check the success rate of stem cells in vitro and in vivo using inorganic scaffold materials in bone regeneration.[10] So far, in vivo studies have been conducted to report evidence about the effect of DPSCs/SHED in bone regeneration. The present study has tried to provide evidence in this field by summarizing the results of animal studies because the comprehensive results can lead to the decision of clinical trials in this field. Therefore, the present study aimed to evaluate enhanced bone regeneration by human adult dental pulp stem cells combined with scaffold.

2. Material and methods

Search strategy and Information sources

The present study was based on the PRISMA 2020-27-item checklist.[11] By giving the keywords stem cells, scaffold, bone regeneration, and human dental pulp stem cells, all articles available in the international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases and Google Scholar search engine were reviewed until November 2023. In addition to this list of sources, the selected articles were screened to find relevant references. The search was done independently by two researchers to avoid bias.

The keywords studied based on the MeSH term were:
(((((("Mesenchymal Stem Cells"[Mesh]) AND "Humans"[Mesh]) AND "Bone Regeneration"[Mesh]) OR "Bone Diseases"[Mesh]) OR "Oral and Maxillofacial Surgeons"[Mesh]) AND "Bone Transplantation"[Mesh].

Study selection criteria

Inclusion criteria

Animal studies, used scaffold, availability of the full text of the article. Studies with incomplete results, case studies, case reports studies, and review articles were excluded.

Selection and data collection process

Two researchers independently collected data from the selected studies using a pre-prepared standard checklist to reduce reporting bias and errors. This checklist included Study specifications, clinical information, and study results.

Study risk of bias assessment

The CAMARADES checklist contained six independent items: randomization, controls, sample size calculation, published after peer review, outcome measure, and statement of potential conflict of interests. Studies that are more effective on the validity of the evaluation results regarding the therapeutic effect (moderate quality); Studies that affect the validity of the evaluation results about the therapeutic effect and change the evaluation results (low quality); Studies in which the results of the evaluation of the therapeutic effect are unclear (very low quality).

Data analysis

STATA/MP. v17 software was used in this meta-analysis. Firstly, heterogeneity between studies was assessed by X2-based Q-tests and I2 tests (25%: low heterogeneity, 25-75%: moderate heterogeneity, and more than 75%: high heterogeneity) or was considered significantly heterogeneous ($p<0.05$). Meta-analysis was performed using mean differences with a 95% confidence interval in meta-analysis.

Study characteristics

Two hundred and thirty-eight animal samples were examined. In most of the selected studies, the treatment period was 8 weeks, and in three studies, it was 6 weeks. Other characteristics are reported in Table 1.

3. Results

Study selection

In the initial search, 190 articles were found, and all articles were entered into EndNote.X8 software; in the first stage, by studying the titles of the articles, the number of 12 articles were deleted due to being repetitive. In the second step, by studying the abstract of 55 articles, 115 unrelated articles (based on the inclusion and exclusion criteria) were excluded from the study. In the third step, after carefully reading the full text of 55 articles, 42 articles were deleted due to inconsistency with the purpose of the study. Finally, 13 articles were used in this study (Fig. 1).

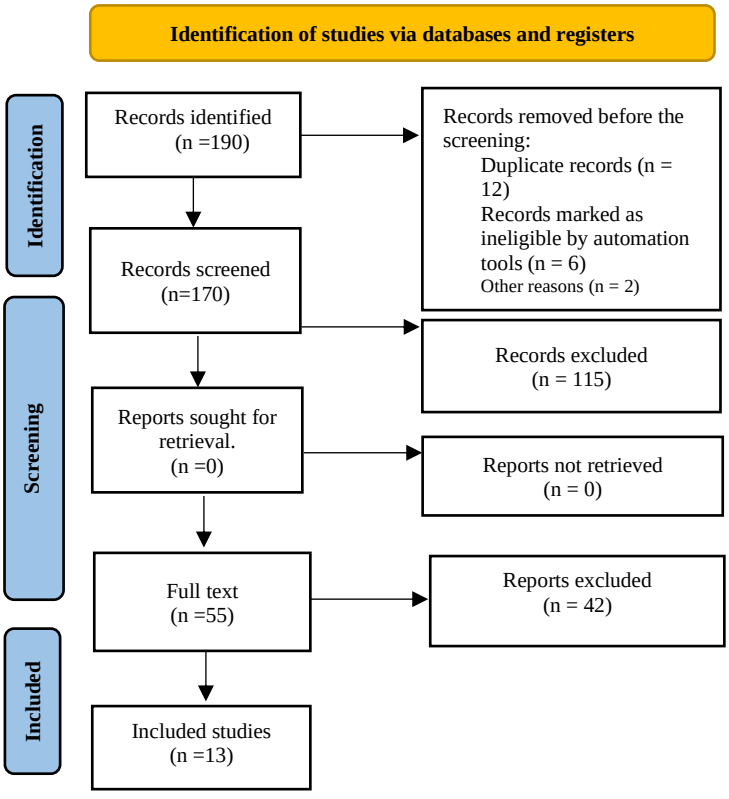

Fig. 1. PRISMA 2020 Checklist.

Table 1. Characteristics of the included studies.

No.	Study. Years	Sample Size	Scaffolds Type	Experimental group	Defect Model of Bone	Follow-up (Weeks)
1	Colorado et al., 2022[12]	20	Polylactideco-glycolide	DPSC + Scaffold	Calvarial defect	10
2	Vater et al., 2022[13]	36	Mineralised collagen Matrix	DPSC + Scaffold	Critical mid-diaphyseal defect	6
3	da Silva et al., 2022[14]	50	Biphasic calcium phosphate	SHED + Scaffold	Calvarial defect	8
4	Zhu et al., 2021[15]	36	Bio-Oss—Collagen	DPSC + Scaffold	Calvarial defect	8
5	Zhang et al., 2020[16]	10	Tyrosine-derived polycarbonate	DPSC + Scaffold	Mandibular defect	23
6	Salgado et al., 2020[17]	4	Collagen–nanohydroxy apatite– phophoserine	DPSC + Scaffold	Subcutaneous implantation	8
7	Bakopoulou et al., 2019[18]	6	Biomimetic chitosan	DPSC + Scaffold	Subcutaneous implantation	10
8	Huang et al., 2019[19]	12	HNTs/GelMA hydrogels	DPSC + Scaffold	Calvarial defect	12
9	Saha et al., 2019[20]	20	Self-assembling β-peptides	DPSC + Scaffold	Calvarial defect	6
10	Jin et al., 2019[21]	15	Puramatrix	DPSC + Scaffold	Mandibular bone defect	6
11	Ansar et al., 2017[22]	5	Alginate hydrogel with $Cacl^2$	SHED + Scaffold	Subcutaneous implantation	8
12	Wongsupa et al., 2017[23]	18	PCL/BCP	SHED + Scaffold	Calvarial defect	15
13	Fang et al., 2017[24]	6	Collagen	SHED + Scaffold	Calvariae cranial defects	8

According to meta-analysis, the mean difference in bone regeneration between the experimental and control groups was 1.69 (MD:1.69; 95% CI 1.00–2.39, P<0.001). According to these findings, bone regeneration in the experimental group was higher than in the control group. According to the test of group differences, a significant difference was observed between the groups under study (p<0.05). BV/TV had marginal effect (MD:5.01 mm^3; 95% CI 2.55 mm 3–7.48 mm^3, P<0.001), new bone formation (MD:2.08 mm^2; 95% CI 0.70 mm2 – 3.47 mm^2, P>0.001) and bone mineral density (MD:0.49 mg/cm^3; 95% CI -0.60 mg/cm3–1.58 mg/cm3, P>0.001) shows no effect. bone formation showed highly significant effect (MD:2.20 mm^2; 95% CI 0.82 mm2–3.58 mm^2, P<0.001) (Fig. 2).

According to meta-analysis, a statistically significant difference was observed considering different groups of scaffolds on bone regeneration in combination with DPSC/SHED (MD:4.84; 95% CI 4.72– 4.95, P<0.001) (Fig. 3).

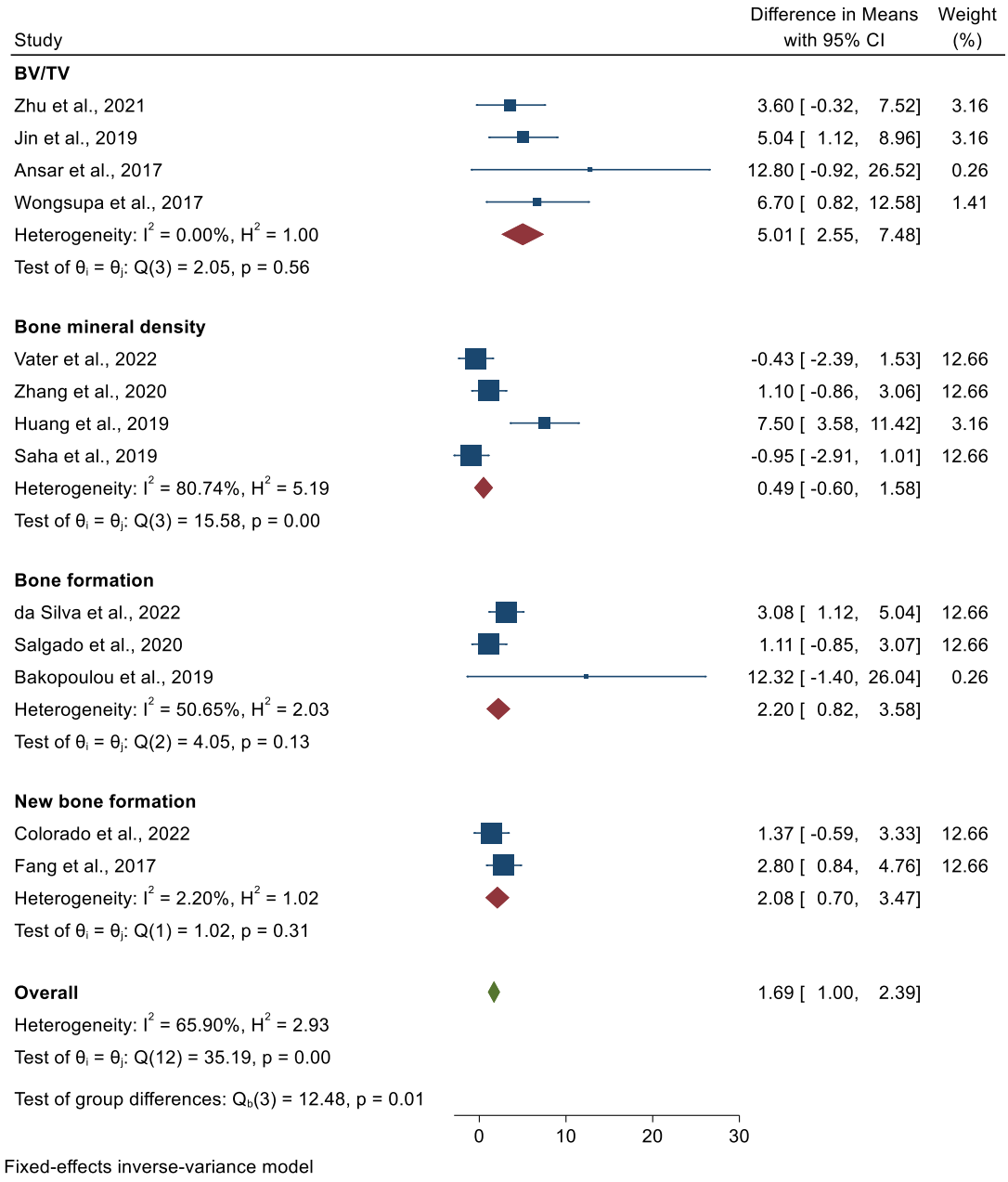

Fig. 2. The forest plot showed a sub-group meta-analysis of the overall effect of bone regeneration between the two groups.

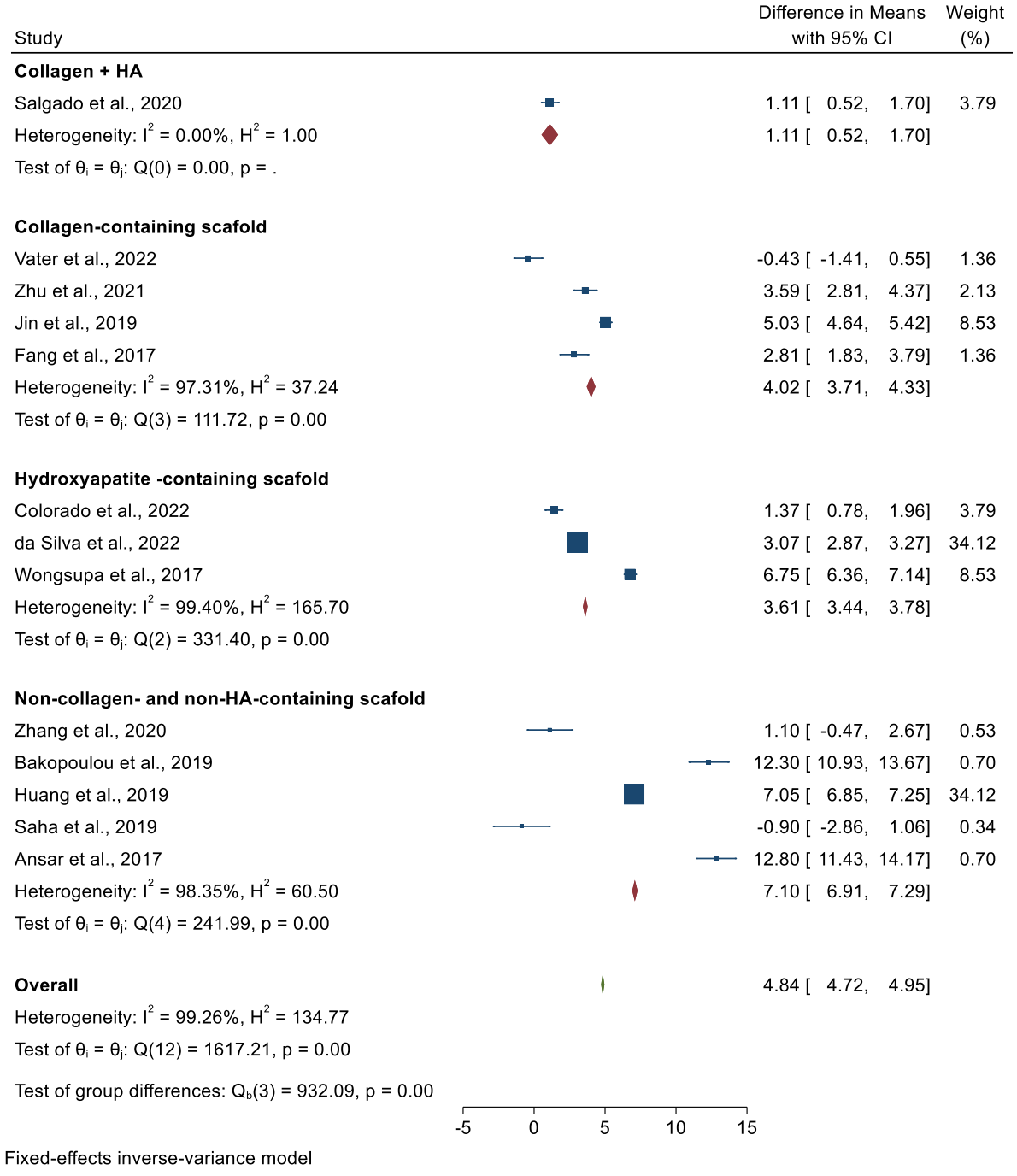

Fig. 3. The forest plot showed a sub-group meta-analysis of bone regeneration using different types of scaffolds between the two groups.

4. Discussion

Before animal studies are performed, all scaffolds used for bone regeneration have been analyzed in vitro.[25] Based on the present meta-analysis, DPSCs/SHED scaffolds were able to significantly increase bone regeneration. Also, a meta-analysis showed that dental pulp stem cells and scaffolds could significantly increase bone formation. As observed, there was a high heterogeneity between the studies, which indicates that the results of the present study should be interpreted with caution. The reason for this could be the difference in the cognitive methodology of the studies; some studies had a poor design, and the sample size was small. All these things can affect the results of the studies and the difference between the average results of the experimental and control groups. There is a need to conduct more studies with a higher sample size and appropriate and ethical cognitive methodology to confirm the current evidence and provide stronger evidence. A study has shown that SHED can increase mineralization capacity compared to DPSC.[26] Another study reported that the results of using SHED and DPSC in new bone formation were similar.[9] These findings are consistent with the present study's results; it was also observed that SHED and DPSC are similarly effective in bone regeneration. Also, the present study's findings indicate that the type of scaffold does not determine the effect of PSCs and SHED in bone

regeneration. Based on the available evidence, it is possible to extract dental pulp stem cells from unerupted wisdom teeth because these teeth are one of the most common methods of oral surgery.[27, 28]

Studies have also shown that using DPSC has been considered to improve the results of dental implants.[29] Currently, studies are investigating the effect of stem cells on bone regeneration, and strong evidence has not been provided.[30] Studies have shown that scaffold + dental stem cells are ineffective in new bone formation.[31-33] A systematic review and meta-analysis study reported that bone regeneration was significantly higher in the scaffold + hDPSC/SHED group than in the scaffold-only group.[34] Considering the differences in the findings of the studies, designing an ideal scaffold is challenging. However, the results of the present study show that integrating dental pulp stem cells with the ability of osteogenesis and the efficiency of the scaffold can increase the formation of new bone or, in other words, ossification. Studies that have been conducted in human clinical trials are very few. However, their findings show the positive effect of using dental pulp stem cells.[35-37] The present study had some limitations, such as the small sample size. Most of the studies did not observe the blinding of the experimental and control groups, which can affect the results of the studies, as well as the design of the studies regarding bone defect models, animal species, Gender, and recovery time.

5. Conclusion

The present meta-analysis showed that dental pulp stem cells and scaffolds can increase new bone formation and accelerate bone formation compared to the control group. Due to the ever-increasing elderly population and the economic burden, the primary need for bone tissue has increased. Based on the results of the present study and previous studies, dental pulp stem cells can be considered a promising option for ossification. More studies and clinical trials are needed to confirm these findings and the effectiveness of treatment based on dental pulp stem cells.

Conflict of Interest

The authors declared that there is no conflict of interest.

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