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Evaluation of the Effect of Stem Cell-based Scaffolds on Bone Regeneration and Formation in Maxillofacial Bone Disorders: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Tissue engineering has provided many hopes for reconstructing bone lesions. For bone engineering, stem cells are cultured on suitable scaffolds under controlled stimulation conditions with growth factors. A scaffold is a temporary matrix for bone growth that provides a specific environment for tissue development and facilitates cell adhesion, growth, and differentiation. The present study aimed to evaluate the effect of stem cell base scaffolds on bone regeneration and formation in maxillofacial bone disorders.

Material and methods: Searching international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases, and Google Scholar search engine based on PRISMA 2020-27-item checklist and keywords Related to the objectives of the study, it was carried out from 2013 to January 2024. The prevalence was equivalent to the rate ratio of bone formation. A model with fixed effect and inverse–variance method was used. All statistical analyses are done using STATA/MP software. v17 was done considering the significance of less than 0.05.

Results: Nine studies were selected according to the inclusion criteria. The fixed-effects rate ratio of bone formation meta-analysis showed that ES = 0.39, 95% CI; 0.34-0.45, p-value < 0.001. the test of group differences showed no statistically significant difference between types of stem cells in the rate ratio of bone formation in maxillofacial bone disorders, and all three types have similar findings (p=0.08).

Conclusions: All three types of stem cells (DPSCs, ADSCs, BMSCs) used in Maxillofacial Bone Disorders showed similar findings in the ratio of bone formation.

1. Introduction

One of the major global health problems is injuries caused by various accidents, especially among teenagers. Such accidents and injuries mainly lead to death or disability in the people involved. These harmful accidents can be road accidents, fights, beatings, injuries caused by sports exercises, accidents at work, and falling from a height.[1] Injuries to parts of the body are more important, and one of these areas, the maxillofacial, includes most of the fractures caused by all kinds of traumas.[2] The area of the maxillofacial is one of the most sensitive parts of the body, which itself contains many vital elements and is also of particular importance in maintaining human beauty. Therefore, the treatment of injuries to it requires high cooperation and group coordination.[3] Also, damage to maxillofacial bone can be due to congenital abnormalities, periodontal disease, or loss of alveolar bone.[4] Replacement bone graft is a method used for maxillofacial bone injuries. Maxillofacial bone damage can be due to congenital anomalies, periodontal disease, or loss of alveolar bone.[5] This method has advantages and disadvantages; the disadvantages of this method are bleeding, painful surgery, and nerve damage, and studies are looking for ways to replace this method.[6] One of the suggestions for replacing the treatment method is the use of stem cells, which have received much attention due to their self-healing, self-renewal, and

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ability to differentiate into different cells.[7] Scaffolds play a key role against progenitor cells in tissue engineering.[8]

Therefore, considering the importance of the issue in today's world, the present study summarizes the findings of studies in the field of stem cell base scaffolds in order to provide good evidence in this field. The purpose of the present study is to evaluate the effect of stem cell-based scaffolds on bone regeneration and formation in maxillofacial bone disorders.

2. Material and methods

Search strategy and Information sources

Searching international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases, and Google Scholar search engine based on PRISMA 2020-27-item checklist[9] and keywords Related to the objectives of the study, it was carried out from 2013 to January 2024. The keywords were standardized in MeSH and used for searching. In addition, the reference list of the selected articles was screened to find relevant studies. The search strategy was (((((((("Osteogenesis"[Mesh]) OR "Eiken Skeletal Dysplasia" [Supplementary Concept]) OR "Bone Regeneration"[Mesh]) OR "Fractures, Bone"[Mesh]) OR "Maxillofacial Injuries"[Mesh]) AND "Stem Cells"[Mesh]) OR "Mesenchymal Stem Cells"[Mesh]) OR "Human Embryonic Stem Cells"[Mesh]) OR "Dental Pulp"[Mesh].

At first, a list of titles and abstracts of all articles searched in the databases under review was prepared. This work was done independently by two researchers. The articles with duplicate titles were removed. Next, the abstracts of the articles were checked to find suitable studies, and all the studies that were searched were saved in EndNote. The software performed X8 software and the rest of the steps.

Study selection criteria

The inclusion criteria of the studies were: 1. All human and animal studies; 2. Any type of stem cells; 3. Stem cells for scaffold in maxillofacial bone disorders. The exclusion criteria were chosen as follows: irrelevant in terms of study design and research topic, studies that did not contain enough information, low-quality studies, and studies with incomplete data.

Selection and data collection process

To reduce reporting bias and errors in data collection, two researchers independently extracted data from the articles using a standard data collection form that had been prepared in advance. This form was first designed by the study team, which included the following items: author name, study title, year of publication, type of study, type of scaffold, type of stem cell used, sample size, statistical population, location of injury, and duration of treatment.

Article quality assessment

SYRCLE's risk of bias tool for animal studies was used to evaluate the quality of the included articles. The resulting SYRCLE for animal studies contains 10 entries. These entries are related to selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.[10]

Meta-analysis

The prevalence was equivalent to the rate ratio of bone formation. The I^2 statistic, used to measure inconsistency, was used to analyze the degree of variation across studies (heterogeneity). Low levels of heterogeneity were defined as I^2=25–49%, moderate levels as I^2=50–74%, and high levels as I^2=75–100%(11). A model with fixed effect and inverse–variance method was used. All statistical analyses are done using STATA/MP software. v17 was done considering the significance of less than 0.05.

3. Results

Study selection

In the first stage of the search, 188 articles were found, and after reviewing the titles of the articles, six duplicate and overlapping articles were removed. Abstract: 166 possible related articles were reviewed, and 144 unrelated articles were identified and eliminated. The full text of the remaining 22 articles was reviewed, and finally, nine suitable articles were selected to enter the meta-analysis stage (Fig. 1).

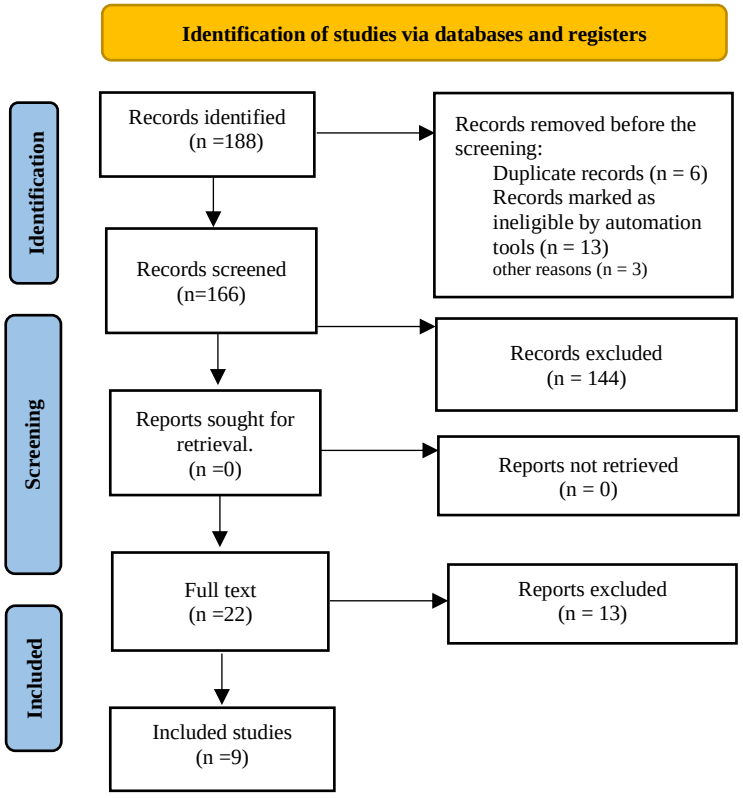

Fig. 1. PRISMA 2020 Checklist.

Study characteristics

One hundred forty animal samples were examined that used dental pulp mesenchymal stem cells (DPSCs), Adipose-derived stem cells (ADSCs), and Bone mesenchymal stem cells (BMSCs) as stem cells. The treatment period was 8 weeks in most of the selected studies, 6 weeks in one new study, and 12 weeks in two studies. Other characteristics are reported in Table 1.

Bone formation

The fixed-effects rate ratio of bone formation meta-analysis showed that ES = 0.39, 95% CI; 0.34-0.45, p-value < 0.001, which means that rate ratio of bone formation using stem cells–based scaffolds was 39% with a significant p-value (Fig. 2). The heterogeneity test showed that Q = 68.20, p-value < 0.001, I^2 = 88.27%, which denotes a high heterogeneity (88.27%) among studies with significant p-value.

Table 1. The characteristics of the selected articles according to the purpose of the study.

No.	Study, Years	Study design	Sample size	Statistical society	Type of stem cell	Scaffold	Lesion location	Duration of treatment (week)
1	Da Cunha et al., 2023[12]	Animal study	28	Rats	DPSCs	Collagen/chitosan	Mandible	6
2	Lee et al., 2021[13]	Animal study	10	Dogs	ADSCs	βTCP	Mandible	8
3	Zhang et al., 2020[14]	Animal study	17	Rats	BMSCs	βTCP	Mandible	8
4	Prahasanti et al., 2020[15]	Animal study	14	Rats	BMSCs	CAS	Mandible	8
5	Lopez et al., 2018[16]	Animal study	5	Rabbits	BMSCs	βTCP	Mandible	8
6	Moser et al., 2017[17]	Animal study	24	Rats	BMSCs	βTCP	Mandible	26
7	Lee et al., 2015[18]	Animal study	28	Rats	ADSCs	PLGA	Mandible	12
8	Alfotawei et al., 2014[19]	Animal study	8	Rabbits	BMSCs	βTCP	Mandible	12
9	Yun et al., 2014[19]	Animal study	6	Dogs	BMSCs	βTCP	Mandible	8

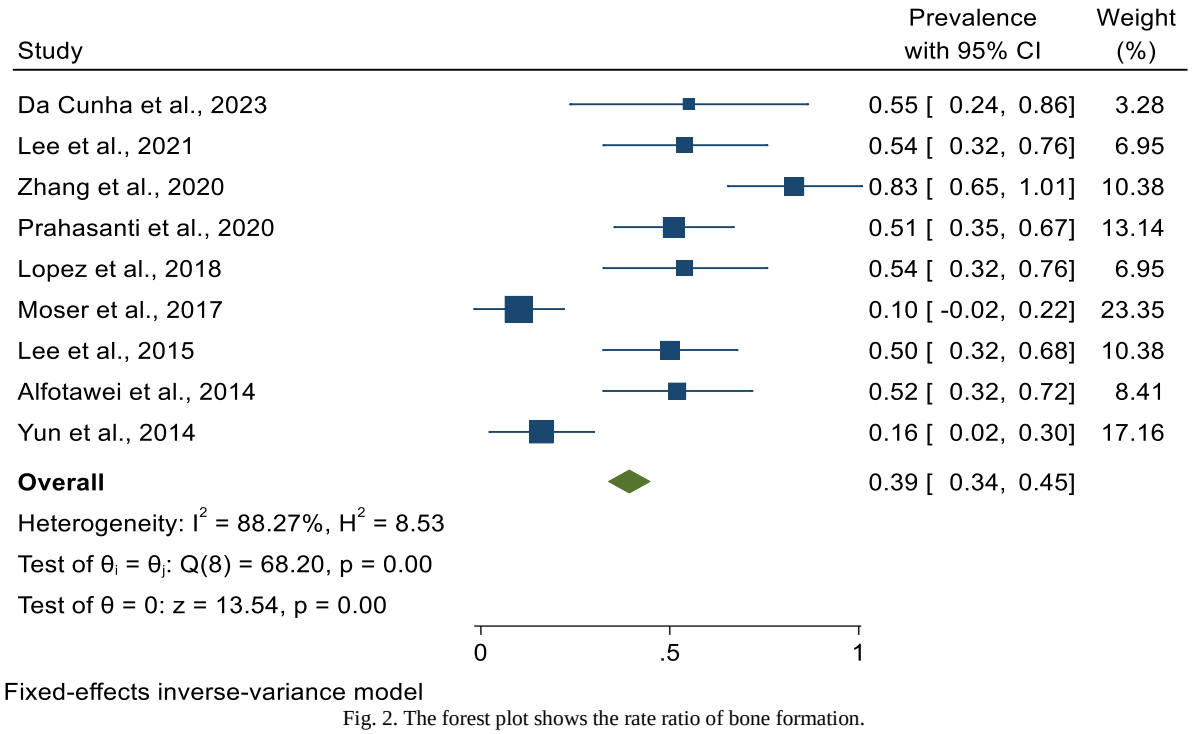

Fig. 2. The forest plot shows the rate ratio of bone formation.

According to subgroup meta-analysis, the rate ratio of bone formation of DPSCs was ES = 0.55, 95% CI; 0.24-0.86, p-value < 0.001, which means that rate ratio of bone formation using DPSCs scaffolds was 55% with a significant p-value (Fig. 3); the rate ratio of bone formation of ADSCs was ES = 0.52, 95% CI; 0.38-0.65, p-value < 0.001, which means that rate ratio of bone formation using ADSCs scaffolds was 52% with a significant p-value (Fig. 3) and rate ratio of bone formation of BMSCs was ES = 0.36, 95% CI; 0.30-0.42, p-value < 0.001, which means that rate ratio of bone formation using BMSCs scaffolds was 36% with a significant p-value(Fig. 3). the test of group differences showed there is no statistically significant difference between types of stem cells in the rate ratio of bone formation in maxillofacial bone disorders, and all three types have similar findings (p=0.08). According to the funnel plots (Fig. 4), publication bias was obvious for the outcomes of bone formation.

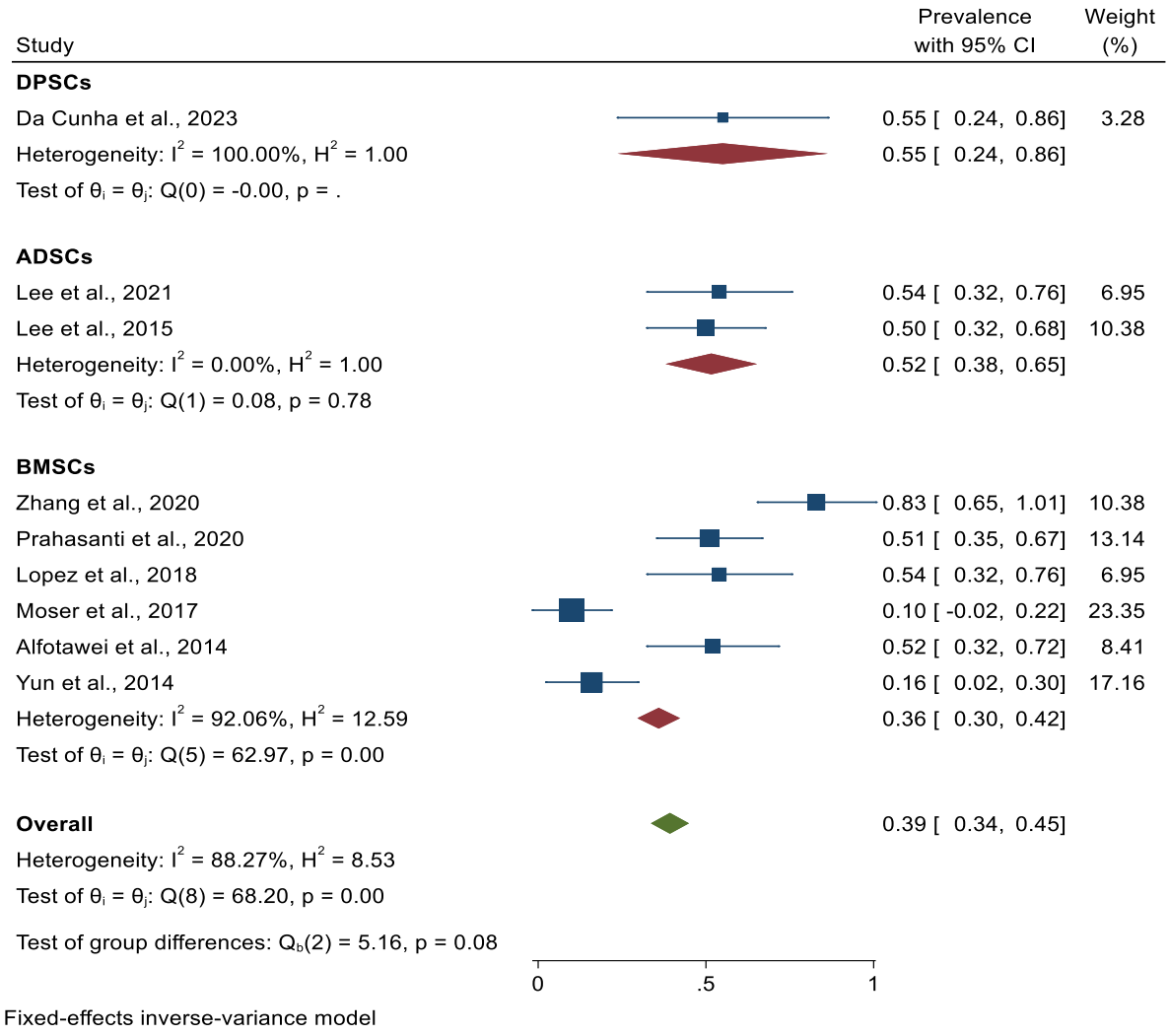

Fig. 3. The forest plot shows the rate ratio of bone formation according to the types of stem cells.

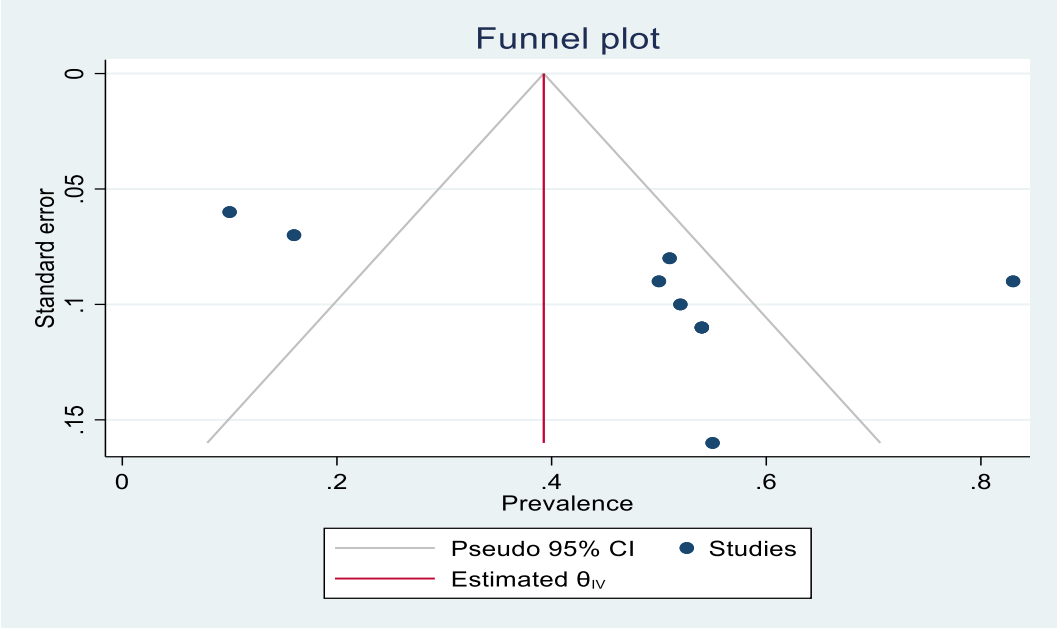

Fig. 4. Funnel plots investigated publication bias in meta-analysis.

4. Discussion

According to the search conducted in the last ten years, few studies have investigated the scaffolding used in the reconstruction of jaw and facial bone lesions. Therefore, the findings of the present study depend on the small number of animal studies, and this shows that It is that more studies should be done to confirm the evidence and reach the ideal treatment, although the scaffold is the key factor in the success of tissue engineering. Most of the selected studies used BMSCs for bone regeneration, and the present meta-analysis showed that the rate ratio of bone formation using BMSC scaffolds was 36%. Also, a meta-analysis showed that the rate ratio of bone formation of ADSCs and DPSCs was 52% and 55%, respectively. A study has shown that the use of a scaffold seeded with mesenchymal stem cells in an animal model can significantly increase osteogenesis compared to the scaffold alone.[20] A study has also shown that the types of stem cells used for bone regeneration are BMSCs.[21] Studies have shown that the use of ADSC aggregates, which affect bone formation, for 3D-printed scaffolds has several advantages. Scaffolds are good mediators for the survival and bone formation of these ADSCs.[22, 23] Some factors should be considered in studies to achieve the desired results in bone tissue engineering. These factors include conducting clinical studies. So far, limited clinical studies have been conducted on humans, and the number of samples in each study was very small. Most studies have been done on the reconstruction of small lesions in small animals. In order to reach results that can be generalized to humans, larger animals with structures and immune systems similar to humans should be investigated. Appropriate selection of control groups can help to better interpret the results and show the effect of each variable. Most of the studies have been done in a short time. Following up the sample for a longer period can improve the results and also show the possible side effects of the substances. In a smaller number of studies, all three components of tissue engineering are placed next to each other. It is necessary to pay attention to the factors necessary to simulate natural restoration and to ensure that these factors are gradually released into the environment.

There are different ways to present the results of research, but it should be kept in mind that the study of factors such as angiogenesis and immunological reactions, which are important factors in bone regeneration, must be done. Also, presenting the results of qualitative ossification can help compare similar studies. Tissue engineering, on the other hand, can theoretically be used in dentistry; this clinical use has not been widespread due to the lack of affordability and considerations related to cell manipulation. However, its prospects attract dentists and researchers. In the present study, in which meta-analysis was performed on the scaffolds used in the reconstruction of bony lesions of the jaw, face, and skull, it was found that there is still a long way to go to reach the ideal treatment. Although scaffolding is considered a key factor in the success of tissue engineering, still after more than twenty years of tissue engineering, an ideal scaffold has not been designed. Most of the studies have been done on the reconstruction of small lesions, and features such as angiogenesis and bone physiology have been considered less. It seems that the future perspective of bone tissue engineering is given to the use of the Rapid Prototyping method to make composite and patient-specific scaffolds from CT and MRI images, along with genetically modified stem cells.

5. Conclusion

Based on the present meta-analysis, all three types of stem cells (DPSCs, ADSCs, BMSCs) used in Maxillofacial Bone Disorders showed similar findings in the ratio of bone formation. The results of the present study can help future findings to increase the design of suitable scaffolds for jawbone tissue engineering in the not-so-distant future. However, more studies with a larger sample size are needed to confirm the evidence.

Conflict of Interest

The authors declared that there is no conflict of interest.

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