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Evaluation of the Effect of Using Adipose Stem Cells in Bone Augmentation in Patients with Jaw Bone Atrophy: A Systematic Review and Meta-analysis

Hassina Shadab [a], Mohammad Eissa Ahmadi [a], Sajeya Karimi [a], Marzia Moez [b], Amena Waziri [a]

[a] *Department of Periodontics, School of Dentistry, Kabul University of Medical Sciences, Kabul, Afghanistan*
[b] *Department of Oral and Maxillofacial Surgery, School of Dentistry, Kabul University of Medical Sciences, Kabul, Afghanistan*

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ABSTRACT

Background and aim: Alveolar ridge bone augmentation is required for patients receiving dental implant therapy who have atrophy of the jaw bone. The latter method does not require bone harvesting, which makes it less invasive during surgery. However, it is not always successful in producing enough bone for dental implant therapy because it does not ensure local osteoblast differentiation and blood flow from surrounding tissues. This research aims to assess the impact of bone augmentation with adipose stem cells in patients with atrophy of the jaw bone.

Material and methods: The use of Google Scholar and international databases like PubMed, Web of Science, Scopus, Sites Direct, Elsevier, and Wiley was necessary to find published articles and scientific proof regarding the impact of adipose stem cell therapy on bone augmentation in patients suffering from atrophy of the jaw bone; the search period was until June 2024. Data were analyzed using STATA software, Version 17. The effect size was measured with a 95% confidence interval (CI), and a fixed effect model and inverse variance method were used.

Results: Six studies were reviewed. The six-month survival rate was 79% (ES 95% CI: 0.10-1.47). The survival rate of augmented bone in patients in the ASCs+ group following jawbone augmentation with bone substitutes containing adipose stem cells was significantly higher ($P < 0.01$) than in the ASCs group.

Conclusions: According to the results, patients with jaw bone atrophy may benefit from using ASCs for bone augmentation on the alveolar ridge.

1. Introduction

When treating periodontitis with bone resorption or severely atrophied jawbones, dental implant therapy typically entails autologous bone transplantation or tissue regeneration with bone substitutes. Because harvesting autologous bone from locations like the ilium is so invasive, using bone substitutes is the preferred method between these two techniques. Nevertheless, bone substitutes limit tissue regeneration due to the absence of osteoblasts, blood vessels, and other cells. So, studies have assessed the application of bone substitutes combined with stem cells derived from bone marrow.[1] However, bone marrow is deficient in stem cells,[2] so adipose tissue, rich in cellular components and can yield positive outcomes when combined with bone substitutes, is becoming increasingly popular as a source of adipose stem cells (ASCs). The use of cultured adipose and bone marrow-derived cells in periodontal regeneration models and the regeneration of different organs and tissues has been studied in clinical research, considering the background mentioned above.[3-5] According to certain research, stem cells derived from adipose tissue can be differentiated into different types of mesodermal cells in vitro.[6] Other studies have shown that these stem cells are simple to extract and can be used to regenerate bone.[7-9] Early skull restoration was documented using non-cultured ASCs obtained by enzymatically treating human adipose tissue,[10] rich in neovessels and osteoblasts. As a result, human cranial reconstruction was carried out using these cells.[11]

Moreover, complete continuity with the skull was observed three months after reconstruction when autologous fibrin glue (AFG) and autologous stem cells were utilized to reinstall cryopreserved skull fragments in patients with a wide calvarial defect following head trauma.[12] Before receiving dental implant therapy, a Dutch research group examined using bone substitutes alone versus bone substitutes combined with ASCs for sinus floor bone augmentation in the bilateral maxillary molar regions. The group also summarized a protocol for regenerative therapy with ASCs in jaw bone regeneration.[13] Bone substitutes combined with ASCs significantly improved bone augmentation at the transplant site compared to the control group, according to a bone biopsy performed by the group during dental implant placement; no untoward events were noted.[14] Given the topic's significance in today's world, the current study attempted to investigate the

* *Corresponding author. Sajeya Karimi*
E-mail address: *sajeyakarimi38@gmail.com*
Department of Periodontics, School of Dentistry, Kabul University of Medical Sciences, Kabul, Afghanistan
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impact of treating jaw bone regeneration with a combination of ASCs and bone substitutes. Thus, this research aims to assess the impact of bone augmentation with adipose stem cells in patients with jaw bone atrophy.

2. Material and methods

Search strategy and data sources

The use of Google Scholar and international databases like PubMed, Web of Science, Scopus, Sites Direct, Elsevier, and Wiley was necessary to find published articles and scientific proof regarding the impact of adipose stem cell therapy on bone augmentation in patients suffering from atrophy of the jaw bone. Keyword searches were used to search these databases: Stem Cell, Stem Cell, Mesenchymal, Mesenchymal Stem Cell, Mesenchymal, Mesenchymal Stromal Cells, Bone Marrow Mesenchymal Stem Cells, Adipose-Derived Mesenchymal Stem Cells, Adipose-Derived Mesenchymal Stromal Cells, Adipose-Derived, Adipose Tissue-Derived Mesenchymal Stromal Cell, Adipose Tissue-Derived Mesenchymal Stem Cell, adipose stem cell transplantation, jaw bone regeneration, alveolar ridge bone augmentation, jaw bone atrophy, dental implant; and medical subject headings (MeSH) terms were also used, which included (((((("Stem Cells"[Mesh] OR "Stem Cell Transplantation"[Mesh]) OR "Mesenchymal Stem Cells"[Mesh]) OR "Adipose-Derived Mesenchymal Stem Cells" [Mesh]) OR "Adipose-Derived Mesenchymal Stromal Cells" [Mesh]) OR "Mesenchymal Stem Cells, Adipose-Derived" [Mesh]) OR "Adipose Tissue-Derived Mesenchymal Stromal Cell" [Mesh]) OR "Adipose-Derived Mesenchymal Stem Cell" [Mesh]) AND "Jaw"[Mesh]) AND "Bone Substitutes"[Mesh]) AND "Survival Rate"[Mesh]) AND "Dental Implants"[Mesh]. The search period was until June 2024.

Additionally, the reference list of procured items was examined to determine which used items were not acquired through the aforementioned channels. Based on inclusion criteria and the PICOS approach, all articles were chosen.

Inclusion and exclusion criteria

Inclusion criteria included patients with jaw bone atrophy in preparation for receiving dental implant therapy (P: Population), bone substitutes mixed with ASCs, treated with bone substitutes alone (C: Comparison), and Studies that reported clinical Efficacy of augmented bone (O: Outcome). All randomized clinical trial studies, cohort studies, case-control and case reports (S: Studies). Excluded from the study were reviews, books, qualitative studies, studies with incomplete results, and scientific publications without full text. Other studies published in languages other than English were also avoided.

Procedures for data collection and selection

A form designed based on the purpose of the research was used to extract data. This form included the first author's name, year, research population, sample size, average age of patients, Type of Regeneration, Site of tissue collection, and Dental implant. After two independent, blind authors reviewed the data, a third independent author assessed the completed form. Every article was added to the End. Note X.8 software, and two authors examined each article's content. Every argument between the two authors was settled by conversation, and when necessary, a third reviewer was consulted. Studies with survival data were given priority for examination.

Risk assessment

For a Randomized controlled trial, the Cochrane risk-of-bias tool (RoB 2) is the suggested instrument for evaluating the risk of bias.[15] Each of the five domains, selection, performance, attrition, reporting, and others, has a judgment associated with it, ranging from high (0-2) to low (5-6) and unclear (3-4).

The quality of the included non-randomized controlled trial was evaluated using the Newcastle-Ottawa scale (NOS).[16] Under the NOS's star scoring system, each study can receive up to nine stars (for retrospective, prospective, and cross-sectional studies). A score of 7-9 indicates high quality, a score of 4-6 indicates high risk of bias, and a score of 0–3 indicates extremely high risk of bias.

Statistical analysis

STATA software, version 17, was used to analyze the data. The I^2 index and P-value <0.1 were employed for the Q test to assess the studies' heterogeneity. Small, moderate, and large heterogeneity are represented by I^2 values of 25%, 50%, and 75%, respectively. The effect size with a 95 percent confidence interval (CI) was applied. The Egger test was used to assess publication bias.

3. Results

Study selection

Initially, a search yielded 194 articles. Upon perusing the titles, it was determined that 56 articles were repetitive and needed to be eliminated. In the second stage, after examining the abstracts of the 111 remaining articles, 86 pieces were eliminated because they needed to meet the study's objectives per the established inclusion and exclusion criteria. In the third phase, a thorough examination of the full texts of the 25 remaining articles followed. This resulted in the removal of 19 articles due to insufficient data, irrelevant content, and non-compliance with the study's objectives. In the end, six articles were included in this research.

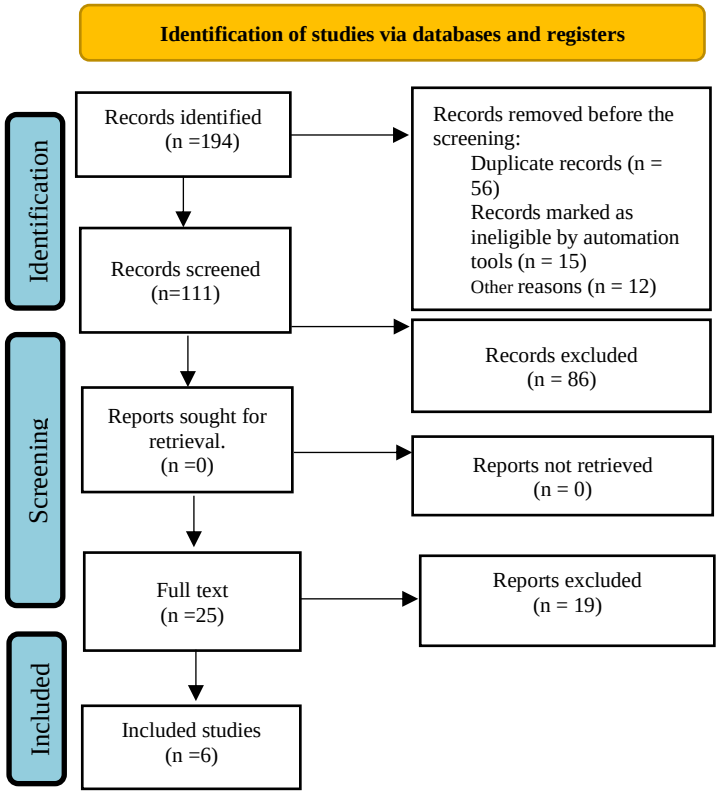

Fig. 1. PRISMA 2020 Checklist.

Study characteristics

The intervention group examined 57 patients (patients who underwent jaw bone augmentation with bone substitutes made from adipose stem cells). Only one study had a control group that examined 20 patients, and in other studies, the control group was considered the study site. Table 1 summarizes the characteristics of the selected studies.

Quality assessment

According to the instruments used to assess the studies' quality, all chosen studies were of high quality, while one RCT study was of moderate quality (Table 1).

Table 1. Summary of patient information.

Study. Years	Study Design	Number of Patients/ Study Side		Mean of Age (Years)	Sex of Patients/ Study Side		Number of Dental Implants	Study Quality
		ASCs+	ASCs-		Female	Male		
Kizu et al., 2024 [17]	Retrospective Study	10	20	60.4	10	20	82	9/9 High
Wu et al., 2023 [18]	Prospective Study	10	6	66	6	4	44	8/9 High
Asahina et al., 2021 [19]	RCT	8	8	54.2	6	2	30	5/6 High
Farré-Guasch et al.,2018 [20]	RCT	10	6	30	6	4	44	5/6 High
Sohrabi et al., 2016[21]	RCT	8	8	20	2	6	NR	5/6 High
Prins et al., 2016 [14]	RCT	10	10	56	6	4	44	4/6 Moderate

ASCs+: patients who underwent jaw bone augmentation with bone substitutes with adipose stem cells; ASCs-: patients who underwent jaw bone augmentation with bone substitutes without adipose stem cells.

Survival rate of augmented bone

The six-month survival rate was 79% (ES 95% CI: 0.10-1.47). When compared to patients who did not receive adipose stem cells (ASCs- group), the survival rate of augmented bone in patients in the ASCs+ group following jawbone augmentation with bone substitutes containing adipose stem cells was significantly higher ($P < 0.01$) than in the ASCs− group. According to the heterogeneity results, there is little variation between the studies ((I^2=0; p=1.00); Q is equal to 0.04) (Fig. 2).

When comparing the results of cohort studies and RCT studies, it was observed that the survival rate at six months was 75% (ES 95% CI: 0.05-1.56) in RCT studies and 88% (ES 95% CI: 0.05-1.56) in cohort studies. CI: 0.43-2.19). Studies showed that bone tissue regenerated better in the ASC+ group after six months (Fig. 3).

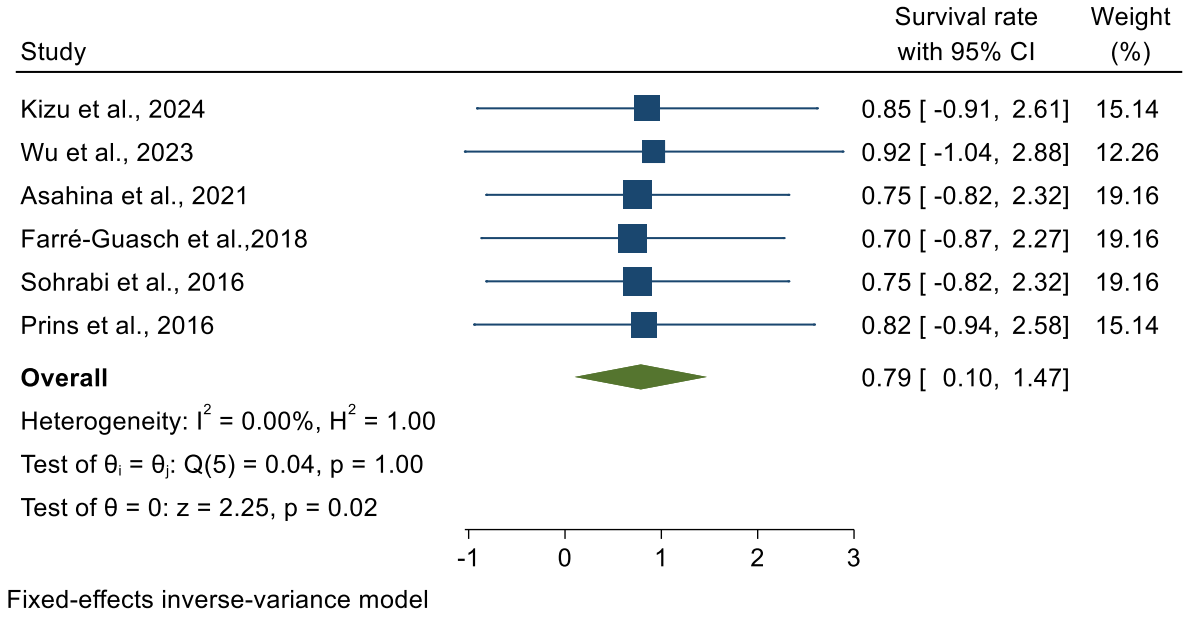

Fig. 2. The forest plot showed a survival rate of the jaw bone with bone substitutes mixed with ASCs.

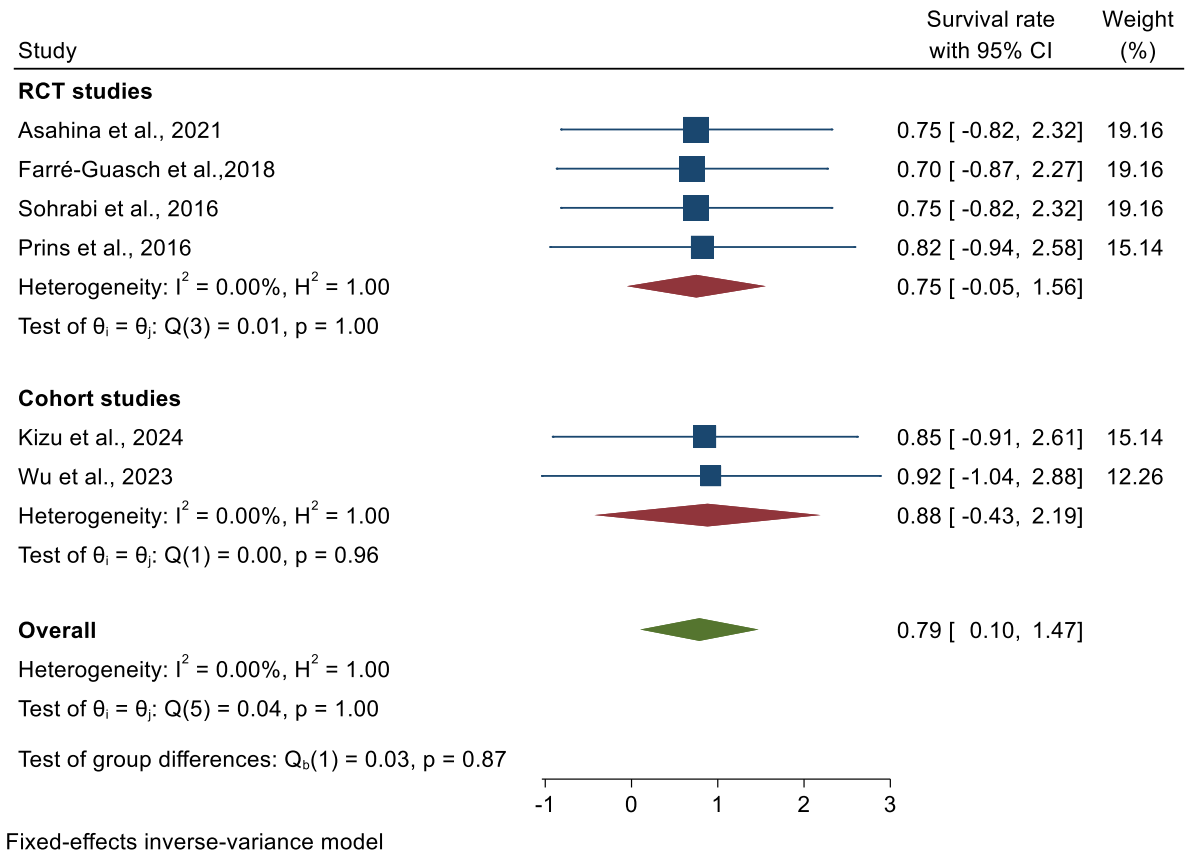

Fig. 3. Comparison of results from cohort studies and RCT studies.

4. Discussion

Due to their autologous origin, ASCs carry a minimal risk of tumorigenesis and no risk of transplant rejection. In contrast to cultured cells, autologous tissue is used to extract ASCs, so contamination is not a concern. Furthermore, the comparatively simple sampling procedure makes the patient less burdened. ASCs have been used to treat a variety of illnesses, including dementia, liver cirrhosis, cerebral infarction, and aesthetic restoration. ASC transplantation is not advised in obese people (BMI > 30), though, as the liquid component that ASCs produce in these people may encourage the growth of cancer cells. Additionally, due to its documented impact on tumorigenesis and tumor progression, it should not be administered to cancer patients.[22] As a result, caution should be used when doing this procedure on patients who pose a risk or are not a good fit. According to our knowledge, this is the first meta-analysis study to assess the impact of bone augmentation with adipose stem cells in patients with atrophy of the jaw bone. Because poor blood flow in the jaw's cortical bone makes it difficult for stem cells and osteoblasts to migrate along microvessels generated in the scaffold created by bone substitute, bone augmentation on the alveolar ridge with bone substitutes alone only occurs laterally, which has a negative effect on bone regeneration. In order to stimulate the MSCs required for bone tissue regeneration, ASCs added to bone substitutes may enhance blood flow from surrounding bone tissue capillaries.[20] According to certain research, ASCs can also differentiate into platelets, which aid in tissue regeneration and repair.[23] These findings imply that ASC transplantation may enhance blood flow from nearby capillaries, causing MSC migration to bone regeneration sites and efficient bone tissue regeneration linked to the activity of ASC-generated platelets.[24] Because of stimulation from different growth factors and cytokines in AFG, combining bone substitutes with ASCs and AFG may cause differentiation of ASCs and peri-augmentation of MSCs into osteoblasts in addition to anchoring ASCs. Studies have also revealed that fibroblast growth factor-2 significantly activates MSCs during remodeling.[17] The morphology and quality of bone tissue would be preserved during bone regeneration, and dental implant therapy would be effectively supported by the presence of elements for tissue regeneration, such as stem cells in surrounding bone induced by ASC transplantation, ASCs, and AFG containing cytokines (growth factors), along with bone substitutes as a scaffold. Specifically, humoral components derived from tissue stem cells have been shown to facilitate tissue regeneration.[25] In recent years, humoral factors secreted from ASCs have been shown to support bone formation through the cytokines osteoprotegerin and vascular endothelial growth factor.[26, 27] These growth factors might influence preexisting osteoblasts to promote the formation of new bone, but more research is needed to understand the precise mechanisms.

Kizu et al., 2024[17] demonstrated that, six months later, the ASCs+ group had a significantly higher rate of survival for augmented bone and a bone density index, measured by the grayscale value in dental cone beam computed tomography, than the ASCs− group. According to histological analysis at six months, in the ASCs+ group, bone tissue regeneration was adequate. Wu et al., 2023[18] reported that the implant survival rate was 92.9% for the study sides. Asahina et al. 2021[19] showed that 27 out of 29 dental implants were incorporated into the regenerated bone. During a 7-year, 10-month follow-up period, on average, dental implants and regenerated bone remained stable. Farré-Guasch et al.,2018[20] reported that ASCs demonstrate a high degree of angiogenic potential, making them very intriguing for other clinical

disciplines and tissue regeneration in the oral and maxillofacial region. Sohrabi et al., 2016[21] showed no discernible statistical difference in bone regeneration between the two groups at the time above points.

On the other hand, bone regeneration increased over time significantly on both sides (with and without ADSCs) at all time points. Two primary restrictions apply to this study. The results must be verified in a larger sample in the future because the study sample was small. Furthermore, research on the in vitro mechanism of bone regeneration in ASCs is necessary to understand this process. Alveolar ridge enlargement with autologous bone grafting is currently the only available option for patients undergoing jaw osteotomy due to severe jawbone atrophy or tumors. This is a highly invasive procedure. Further research is needed as patients may benefit from effective bone regeneration through jawbone augmentation using ASC transplantation and bone replacement.

5. Conclusion

The results of the present meta-analysis showed that autologous stem cells (ASCs) combined with bone substitutes improve bone augmentation and regeneration outcomes to a greater extent than when used in isolation. With the addition of ASCs, bone density increases, and bone loss is reduced over time compared to the traditional method. According to these results, alveolar ridge enlargement by autologous stem cell transplantation is a valuable approach that can improve dental implant therapy.

Conflict of Interest

The authors declared that there is no conflict of interest.

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