

Alveolar Reconstruction Using Stem Cells in Patients with Cleft Lip and Palate: A Systematic Review

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Abstract

Mesenchymal stem cells (MSCs) isolated from dental tissues have also been studied extensively recently due to their relatively easy availability. The researchers have been working on improving a method for regenerating alveolar bone in patients with cleft lip and palate utilizing mesenchymal stem cells isolated from human bone marrow (hBMSCs). A systematic literature review from 2010 to 2022 was performed using PubMed, Medline, and ScienceDirect databases. The keywords used were "cleft lip," "cleft palate," "and stem cells," and "alveolar reconstruction." In addition, the PRISMA flowchart was used to describe the selection process of searched articles. A total of 9 studies were included in this systematic review, out of which the majority revealed successful treatment of cleft lip and palate using various kinds of stem cells. Although various types of stem cells have shown encouraging outcomes regarding bone regeneration and the treatment of cleft lip and palate, the most effective was mesenchymal stem cells, followed by adipose stem cells.

Keywords: Cleft lip, Cleft palate, Stem cells, Alveolar reconstruction

INTRODUCTION

Researchers have isolated stem cells from various sources, including bone marrow, adipose tissue, skin, and umbilical cord, and studied them for their potential to proliferate and differentiate into other cell types, thereby regenerating damaged tissues. Mesenchymal stem cells (MSCs) isolated from dental tissues have also been studied extensively recently due to their relatively easy availability. In 2000 [1], human dental pulp stem cells (hDPSCs) were first isolated. The stem cells from human exfoliated deciduous teeth (SHED) were isolated in the subsequent three years. Additionally, apical papilla and periodontal ligament stem cells were isolated and characterized [2]. Among them are SHED, derived from the pulp of deciduous teeth, tissues typically thrown away for clinical and biological reasons. As a result, SHED is a readily available and potentially effective cell source for tissue regeneration [3].

A cleft lip or palate is the most frequent congenital orofacial anomaly. Most patients will need alveolar bone grafting before beginning orthodontic treatment and again during treatment. Autogenous iliac bone grafting is the traditional method for closing bone defects at the alveolar cleft. However, the extensive surgical invasion creates severe hypoesthesia and pain at the donor site following surgery. Also reported are iliac bone fractures, infections, and hematomas [4]. Iliac bone harvesting is a major surgical procedure, even for young patients. This has led to the hopeful expectation of the eventual development of a less

invasive technique. In this respect, the researchers have been working on improving a method for regenerating alveolar bone in patients with cleft lip and palate utilizing mesenchymal stem cells isolated from human bone marrow (hBMSCs). Dogs with an artificial alveolar cleft had their bone regrown after receiving hBMSC transplants, allowing for the orthodontic migration of teeth into the newly formed bone [5]. However, patients are still forced to undergo invasion since puncturing the iliac bone is required to harvest cells. Thus, it is necessary to investigate a different cell source for alveolar bone rebuilding [6].

In cell therapy, stem cells are injected into a patient, whereas stem cells are embedded in scaffolds in tissue engineering. Stem cells are helpful in a variety of contexts because they differ from differentiated cells in several key

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ways: (1) they can be harvested in more significant numbers; (2) they have a much higher proliferation capacity; (3) they can be cultured for a long time; (4) they can go through senescence and then differentiate into a variety of desired cell phenotypes; and (5) they can support the vascularization of scaffolds. Although current clinical stem cell techniques have the potential to cure a variety of illnesses, including organ failure, congenital structural defects, tissue loss, and organ transplantation or autologous tissue transfer [7], they also have significant limitations, such as immune rejection, organ shortages, allergic responses, and damage to healthy tissues after therapy [8]. Therefore, modern regenerative treatments have centered on stem cell utilization for tissue regeneration and organ replacement [9].

databases. The keywords used were "cleft lip," "cleft palate," "and stem cells," and "alveolar reconstruction." In addition, the PRISMA flowchart was used to describe the selection process of searched articles.

MATERIALS AND METHODS

A systematic literature review from 2010 to 2022 was performed using PubMed, Medline, and ScienceDirect

Table 1. Inclusion and exclusion criteria

No	Inclusion criteria	Exclusion criteria
1.	Case-control, randomized control studies, systematic reviews.	Expert opinions or narrative reviews
2.	Published between 2010 and 2022	Out of the specified time range
3.	Studies including stem cells for the alveolar regeneration	Studies using methods other than the stem cells
4.	English language of publication	Language other than English
7.	In vivo (humans)	In vitro

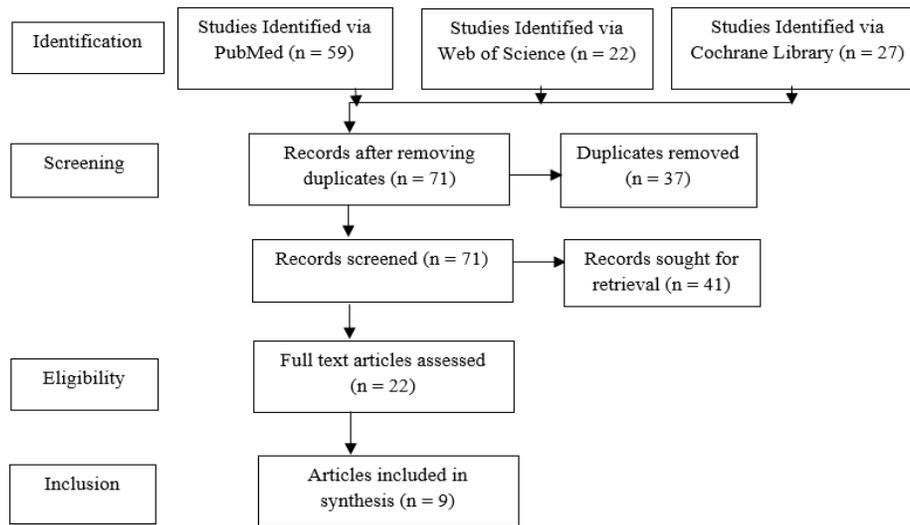


Figure 1. PRISMA Flow Diagram

Risk of Bias Assessment

The Cochrane risk of bias assessment method was used to assess the quality of the studies included.

Table 2. Summary of Cochrane Risk of Bias Assessment

Study	Selection Bias/Appropriate control selection/baseline characteristics similarity	Selection bias in randomization	Selection bias in allocation concealment	Performance-related bias in blinding	Reporting bias/Selective reporting of outcomes	Detection bias Blinding outcome assessors	Accounting for confounding bias
Alamoudi <i>et al.</i> , (2017)	+	+	+	+	+	+	-
Stepanova <i>et al.</i> , (2017)	+	+	+	+	-	+	-
Tanikawa <i>et al.</i> , (2020)	+	+	+	+	+	-	+
Vatankhah <i>et al.</i> (2018)	+	+	+	+	+	+	-

Toyota <i>et al.</i> , (2021)	+	-	+	+	+	+	+
Martín-del-Campo <i>et al.</i> , (2019)	+	+	+	-	+	+	+
Bueno <i>et al.</i> , (2011)	+	+	+	+	+	-	+
Arango <i>et al.</i> , (2014)	+	+	+	+	+	+	-
Schreurs <i>et al.</i> , (2020)	+	+	+	+	+	-	+

RESULTS AND DISCUSSION

Alamoudi *et al.* (2017) [10] investigated that MSCs are an essential and potent tool in regenerative medicine. Tissue engineering uses a combination of stem cells, appropriate scaffolds, and tissue regeneration to give an appealing alternative for facilitating both hard and soft tissue recovery. AT-MSCs have gained popularity and luster in regenerative medicine owing to their angiogenic characteristics, the production of different cytokines with immunomodulatory properties, and wound-healing powers. Furthermore, a high cell count results in adipose tissue aspirate with decreased discomfort and donor site morbidity. MSCs extracted from bone aspirate at a volume of 10-40 ml of marrow, on the other hand, resulted in a low number of cells with significant discomfort and donor site morbidity.

In a study by Stepanova *et al.* (2017) [11], six individuals were chosen to evaluate the influence of MSCs on bone tissue development in young patients with diverse kinds of cleft palate, using autologous MSCs, 3–4 weeks before the scheduled operation. All six patients who were treated with MSCs had positive outcomes. The oral and nasal cavities were separated. The palatopharyngeal ring's function was maintained. The continuity of the upper jaw's alveolar process was repaired, and the mouth vestibule fissure was removed in young patients with unilateral and bilateral cleft palates. At the follow-up X-ray examination following the operation, new tissue was discovered in the location of the bone defect after the application of cellular technologies, comparable to the bone tissue based on density. The density varied from 65 to 110 HU on the Hounsfield scale. Stepanova *et al.* studied the short-term and long-term treatment outcomes of young children with congenital cleft palates. During the postoperative phase, there were no significant variations in the wound healing time.

Tanikawa *et al.* (2020) [12] analyzed the effect of deciduous dental pulp stem cells on maxillary alveolar reconstruction in patients with cleft lip and palate. Six patients, ranging in age from 8 to 12, were examined. For bone healing assessment, a computed tomography (CT) was performed. There were no surgical complications among DDPSC patients. In group one, 37.5% had substantial edema in the early postoperative period, whereas 87.5% experienced severe donor site aches by week two. Preoperative and postoperative exams demonstrated that all six patients who received bone tissue engineering alveolar bone grafts had a progressive alveolar bone union. No patients received DDPSC with 250 mg Bio-Oss Collagen and had partial or

whole graft loss, wound disintegration, or ectopic bone growth.

Vatankhah *et al.* (2018) [13] obtained MSSCs cultivated from the human umbilical cord and intermittently injected them into ten newborns. Specimens are tested with an inverted microscope. After a year, this condition had much healed, the space between the two lips had closed, and the cleft palate of these newborns was improving with continued therapy. According to tests and research, extracting and cultivating mesenchymal stem cells from the cord takes less time. Furthermore, this procedure treats up to 90% of the cells generated in this manner with no adverse effects.

In the research by Toyota *et al.* (2021) [14], surgical procedures are undertaken from infancy through childhood to achieve bone bridge development and continuous structure between alveolar clefts. Human umbilical cords were taken after permission from five healthy full-term pregnant women aged 25 to 38 who had had a cesarean section at a maternity clinic. Micro-computed tomography and histological staining revealed that UC-MACS cells infused with HA Col generated more abundant bone growth between the experimental alveolar clefts than HA Col implantation alone. Cells immunopositive for osteopontin collected along the bone surface, with some becoming lodged in the bone. Immunopositive cells for human-specific mitochondria were aligned along the newly created bone surface and inside the new bone, suggesting that UC-MACS cells contributed to the development of bone bridges across alveolar clefts. These results suggest that human umbilical cords constitute a dependable bioresource and that UC-MACS cells may help with alveolar cleft restoration.

The investigation by Martín-del-Campo *et al.* (2019) [15] in which adipocyte stem cells (ADSCs) appeal to musculoskeletal tissue engineering applications such as cleft lip and palate. The secondary alveolar cleft osteoplasty performed during the mixed dentition stage is the standard treatment for repairing alveolar cleft defects. Martín-del-Campo *et al.* recommended using fatty tissue in maxillary alveolar cleft abnormalities because of its differentiation potential, ease of access to this source of cells, and capacity to grow in vitro quickly. In addition, the authors investigated the ability of ADSCs seeded in biphasic hydroxyapatite/calcium triphosphate (HA/TCP) bone substitutes to repair maxillofacial bone defects, concluding that they were a practical option for the reconstruction of

human maxillofacial bone defects in the case of limited autograft availability or morbidity in the donor site.

The research was done by Bueno *et al.* (2011) [16], in which the primary goal of the work was to see whether there were any persistent changes in gene expression profiles between mesenchymal stem cells from NSCL/P patients and controls. Bueno *et al.* got the mRNA from DPSC was used to validate the microarray expression data by qRT-PCR for a more significant number of genes. In addition, 16 more healthy controls and 13 people with NSCL/P had cultures taken. The transcriptomes of six dental pulp stem cell (DPSC) cultures from NSCL/P patients and six controls were compared in this study. Most of the cell cultures (>90%) showed positive labeling for cell adhesion (CD29, CD90) and mesenchymal stem cell markers (SH2, SH3, SH4) but were negative for endothelial and hematopoietic cell markers. Furthermore, the microarray studies included two NSCL/P patients and three control cell cultures previously proven to differentiate into bone, muscle, cartilage, and fat following in vitro stimulation. As a result, the cell populations employed in this investigation had the characteristics of stem cells.

Arango *et al.* (2014) [17] determined in their research that using SCs and the optimal scaffold for cleft lip patients is little known. Research has focused chiefly on utilizing SCs and scaffolds for alveolar crest rebuilding to replace the

more invasive iliac bone marrow transplant surgery. The child was five months old at the time of surgery and had the following test findings. The aim of utilizing SCs on these individuals is to reduce donor site movement and postoperative problems. To our knowledge, the use of SCs as a coadjuvant in cleft lip surgery has not been documented in the scientific literature. The goal of the research was to describe a case of a cleft lip patient in whom Arango *et al.* employed SCs as a surgical coadjuvant. The patient's lip usually healed, with minimal irritation around the surgery site lasting a few days and dissipating. There was no infection or excessive edema.

Schreurs *et al.* (2020) [18] analyzed in the study that fibrosis and scarring often impede cleft palate surgery's functional and cosmetic results. Schreurs *et al.* addressed emerging tissue engineering technologies for promoting muscle and skin regeneration while reducing scarring. Umbilical cord blood stem cells are a potential, safe, and noninvasive source of stem cells that can be coupled with anti-inflammatory and antifibrotic compounds in a scaffold. Preconditioning stem cells with cytoprotective chemicals before applying them to the wound region may boost stem cell survival and contribute to a regeneration milieu. This unique method is expected to promote muscle and skin regeneration after cleft repair, resulting in a superior functional and cosmetic outcome.

Table 3. Summary of the findings taken from included studies.

Author's name	Specimens	objectives	techniques	Results
Alamoudi <i>et al.</i> , (2017) [10]	NA	To determine the effect of the involvement of mesenchymal stem cells from bone marrow and adipose tissue in the repair of cleft lip and alveolus	tissue engineering	AT-MSCs and BMMSCs may be an appropriate substitute for the future conventional intrusive procedure. They both showed positive results when used in reconstructive therapies. Some differences exist between them, but the most important one is; the ease of collection as well as less donor-side morbidity
Stepanova <i>et al.</i> , (2017) [11]	6	To evaluate the influence of MSCs on bone tissue development in young patients with diverse kinds of cleft palate	X-ray,	Tissue engineering helps treat the congenital pathology of MFA. There are good prospects for using MSCs for the surgical treatment of extensive defects in the facial skeleton.
Tanikawa <i>et al.</i> , (2020) [12]	6	To determine the effect of deciduous dental pulp stem cells for maxillary alveolar reconstruction in patients with cleft lip and palate	computed tomography (CT)	Stem cell therapy results in satisfactory bone regeneration with dental eruption and reduced morbidity compared to traditional iliac crest bone grafting and rhBMP-2.
Vatankhah <i>et al.</i> , (2018) [13]	10	To analyze the effect of mesenchymal stem cells of the umbilical cord on the treatment of cleft palate in children	inverted microscope	This procedure treats up to 90% of the cells generated in this manner with no adverse effects.
Toyota <i>et al.</i> , (2021) [14]	5	To achieve bone bridge development and continuous structure between alveolar clefts using human umbilical cords, mesenchymal cells	Micro-computed tomography	UC-MACS cells infused with HA Col generated more abundant bone growth between the experimental alveolar clefts than HA Col implantation alone.
Martín-del-Campo <i>et al.</i> , (2019) [15]	5	Adipocyte stem cells (ADSCs) appeal to musculoskeletal tissue engineering applications such as cleft lip and palate	tissue engineering, osteoplasty	Adipocyte stem cells (ADSCs) are an effective option for reconstructing human maxillofacial bone defects in the case of limited autograft availability or morbidity in the donor site.

Bueno <i>et al.</i> , (2011) [16]	13	The primary goal of this work was to see whether there were any persistent changes in gene expression profiles between mesenchymal stem cells from NSCL/P patients and controls	qRT-PCR	Most of the cell cultures (>90%) showed positive labeling for cell adhesion (CD29, CD90) and mesenchymal stem cell markers (SH2, SH3, SH4) but were negative for endothelial and hematopoietic cell markers.
Arango <i>et al.</i> , (2014) [17]	one	The purpose was to discuss the effect of SCs as a surgical adjuvant in repairing a cleft lip.	surgery	The patient's lip healed normally, with minimal irritation; there was no infection or excessive edema.
Schreurs <i>et al.</i> , (2020) [18]		This unique method is expected to promote muscle and skin regeneration after cleft repair.	tissue engineering	Preconditioning stem cells with cytoprotective chemicals before applying them to the wound region can boost stem cell survival and contribute to cleft regeneration.

Compared to BM-MSCs, AT-MSCs had enhanced attachment and proliferation abilities *in vitro*. While it takes BM MSCs two to three weeks to fuse after collection, AT-MSCs take just two to three days. Proliferating cell nuclear antigen (PCNA), a protein whose presence is inversely proportional to the proliferation rate, is identified by Western blotting and cell counting. On day 7, AT-MSCs multiplied at a pace that was much higher than that of BM-MSCs. Under certain circumstances, AT-MSCs have shown strong adhesion properties and the potential to undergo multiple lineage differentiation into several cell types, like osteoblast, chondroblast, etc. [19].

The lack of problems after surgery, the return of palatopharyngeal ring function, the separation of the oral and nasal cavities, and radiographic evidence of bone tissue growth in the upper jaw defect all point to a successful outcome. Acceptable results were no problems after surgery, the palatopharyngeal ring worked as it should, and the oral and nasal canals were separated [20].

Still, 33% of patients in the stem cell group had canine impingement. Compared to the estimated 1-2% frequency of impacted canines in the general population, individuals with alveolar clefts have a 20-fold greater risk for canine impaction, depending on canine location. This finding agrees with the previous reports of 35% and 18% impaction of canines in individuals with clefts [21, 22].

Although autogenous bone transplant remains the gold standard for treating bone defects like the alveolar gap, the research found that it is increasingly common to use bone from somewhere else in the body, often the pelvis, a leg, or a rib. Some potential adverse outcomes are infection, gait abnormalities, sensory disruptions, and other organ birth problems. Using tissue engineering methods on autogenous bone is challenging because of the risk of severe morbidity. Nevertheless, this alternate method may achieve the necessary clinical outcomes and bone growth [23].

The hUCMSCs have low immunogenicity and an immunomodulatory effect, making them an excellent choice for regenerative medicine. However, *in vitro* studies have shown that hUCMSCs cannot stimulate the growth of allogeneic PBMCs or suppress their immunological

responses. It was also shown that hUCMSCs did not express the immune-related molecules CD40, CD40 ligand, CD80, CD86, or primary histocompatibility complex class II molecules [24].

Because adult stem cells may differentiate into various cell types and can replenish themselves, tissue engineers have been able to utilize them to repair damage to the head and face. For musculoskeletal tissue engineering projects like cleft lip and palate repair, adipocyte stem cells (ADSCs) are highly sought after. For example, adipose tissue has been suggested for use in the repair of maxillary alveolar cleft abnormalities because of its capacity for differentiation, its accessibility, and its ability to increase *in vitro* [25].

The embryonic-to-adult transition (EMT) is a crucial process underlying palatal fusion. Loss of cell, cell adhesion, disruption of basal laminae, and enhanced cell invasion and mobility occur via a controlled series of events influenced both by the extracellular environment and the gene expression program of the cell. The 87 DEGs include 15 genes involved in EMT. The researchers also improved biological processes related to cell division, migration, and invasion. These are all typical phenotypic effects of genes that are involved in EMT [26].

Adult stem cells (ASCs) have been discovered and extracted from various adult tissues, including bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas, cornea, adipose tissue, and dental pulp. Therapeutic applications of ASCs include a broad spectrum of diseases where tissue and organ replacement or repair is necessary to restore shape and function. Therefore, stem cells, growth factors, and scaffolds are essential when using this technique on people or animals [27].

Isolating MSCs from the baby's bone marrow or adipose tissue is a highly intrusive process that carries the risk of infection, bleeding, and persistent pain. Furthermore, the cost of harvesting and growing cells in a lab is high. Accordingly, new locations to get MSCs are required. A quick, painless, and risk-free operation is performed to extract cord blood cells from a human newborn. Isolating mesenchymal stem cells from cord blood and preserving them for later use is a straightforward process. Since

prenatal ultrasound screening enables early diagnosis of an aperture in the 11th to 13th week of gestation, the preservation of the umbilical cord (blood) following delivery may be planned early. It can be regarded as a new approach to improving cleft surgery. The umbilical vein and the placenta are viable sources for collecting cord blood [28].

CONCLUSION

Although various types of stem cells have shown encouraging outcomes regarding bone regeneration and the treatment of cleft lip and palate, the most effective was mesenchymal stem cells, followed by adipose stem cells. Therefore, there is a need for further investigation regarding the successful regeneration resulting from using bone marrow stem cells.

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ETHICS STATEMENT: This study fulfills the ethical requirements of Riyadh Elm University.

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