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Original Article

Exploring the Role of Adipocyte Stem Cells in Cleft Lip and Palate Management: A Systematic Review

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ABSTRACT

Adipocyte stem cells (ADSCs), a type of mesenchymal stem cell sourced from adipose tissue, play a significant role in the advancement of novel therapies due to their proven efficacy in developing new treatments. These pluripotent cells have the potential to differentiate into various cell types, including adipocytes (fat cells), myocytes (muscle cells), osteocytes (bone cells), and neurons (nerve cells). To assess the role of ADSCs in the treatment of cleft lip and palate, a systematic review of literature published from 2012 to 2022 was conducted using databases such as PubMed, ScienceDirect, and Medline. The search focused on keywords such as "cleft lip treatment,", "adipocyte stem cells," and "cleft palate treatment." Despite the small number of relevant studies, the findings suggest that ADSCs have shown promise in the management of cleft palate, with satisfactory outcomes in certain cases. However, the current evidence remains insufficient to support the widespread clinical application of ADSCs for routine use by oral surgeons in cleft palate reconstruction.

Keywords: Cleft palate, Cleft lip, Adipocyte stem cells, Systematic review.

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Introduction

The cleft palate is one of the most common craniofacial abnormalities seen in newborns. This condition, which can cause significant challenges in speech, feeding, and breathing, not only affects appearance but also impairs functional abilities. Clefts are congenital defects marked by an abnormal gap in the alveolus, upper lip, or palate, and are often referred to as harelip. The terms cleft palate, cleft lip, or cleft lip and palate are more appropriate for describing these conditions [1, 2].

Cleft lip and palate (CLP) are among the most frequently observed congenital defects that may require speech therapy. These defects result from incomplete fusion of the palatal shelves during fetal development. Treatment of CLP greatly improves both the cosmetic and functional aspects of the condition. Proper preparation for cleft lip surgery is critical, as the surgeon has a limited window of opportunity to perform the procedure accurately. Incisions are carefully marked, and the treatment plan is devised based on precise anthropometric measurements [3].

The development of CLP can be attributed to various factors, and it remains the most prevalent congenital condition worldwide. In some populations, like those of Asian and Native American descent, CLP occurs in about 1 in 500 births, whereas in European populations, it affects approximately 1 in 1,000 births [4].

Adipocyte stem cells (ADSCs), a type of mesenchymal stem cell derived from adipose tissue, have the unique ability to self-renew and differentiate into a wide range of cell types. These pluripotent cells can generate fat cells (adipogenesis), bone cells (osteogenesis), muscle cells (myogenesis), and neurons (neurogenesis).

ADSCs hold great promise in advancing new therapeutic approaches and have shown potential in regenerative medicine. This study also highlights some of the risks associated with using ADSCs in the treatment of neoplastic diseases [5-7].

A routine mid-pregnancy scan, usually conducted between the 18th and 21st week of gestation, often identifies a cleft lip. However, detecting a cleft palate through ultrasound can be challenging, and some cleft lips may not be visible in this type of scan [8, 9].

A cleft lip or palate occurs when the structures forming a baby's upper lip or palate fail to join properly during fetal development. The exact cause for this occurrence remains unclear in many cases. It is important to note that it is very unlikely that any actions or inactions during pregnancy are responsible for this condition. Several factors may contribute to the development of cleft lip and palate, including:

• The genetic background of the child (though most cases are isolated occurrences).
• Smoking or alcohol consumption during pregnancy.
• Obesity during pregnancy.
• Inadequate prenatal folic acid intake, the use of certain anti-seizure medications, and steroid tablets in the early stages of pregnancy [10, 11].

Cleft palate repair often requires bone grafts, commonly using autologous cancellous bone to address the hard tissue defect. However, the challenge lies in the grafts' failure to properly integrate with the host bone, leading to eventual collapse. To overcome these issues, tissue engineering frequently employs multipotent cells and biomaterial scaffolds. In this study, we present the cell sheets's development derived from human mesenchymal stem cells (hMSCs) and stem cells from human exfoliated deciduous teeth (SHEDs) for promoting bone healing in cleft palates. These cell sheets demonstrated osteogenic potential through in vitro calcification [4].

By manipulating in vivo niche factors, like low oxygen levels, reactive oxygen species production, and the activation of platelet-derived growth factor receptor signaling, we expect synergistic improvements in the yield of adipose-derived stem cells (ASCs) and a reduction in production costs. Furthermore, preconditioning ASCs with these niche elements may enhance their regenerative capacity before transplantation. However, the ASC niche is complex, and there are still aspects that are not fully understood [12, 13].

Stem cells play a pivotal role in regenerative medicine and are essential for clinical therapies. Mesenchymal stem cells (MSCs), particularly those derived from bone marrow, are known for their strong osteogenic capabilities. Additionally, SHED cells, have demonstrated remarkable osteogenic potential. SHED cells have been shown to effectively heal critical-size calvarial defects in mice through osteogenic differentiation [14, 15].

Both dental and non-dental mesenchymal stem cells have shown promise in regenerating the maxilla, mandible, periodontal ligaments, tooth pulp, enamel, dentin, salivary glands, palates, cleft lips, and other craniofacial structures. This innovative approach holds great potential for advancing research into oral mucosal disease treatment using stem cells [16-19].

Research Assumptions

Adipocyte stem cells are believed to be a highly effective treatment modality for patients suffering from palate and cleft lip, offering significant potential in improving patient outcomes.

PICO Framework

The study focuses on individuals diagnosed with palate and cleft lip, evaluating using adipocyte stem cells as the primary intervention. In comparison, other treatment options that do not involve adipocyte stem cells serve as the control. The main objective is to assess how well adipocyte stem cells can treat palate and cleft lip.

Study Objectives

This review aims to comprehensively assess the effectiveness and success rates of adipocyte stem cells when used to treat palate and cleft lip. By analyzing available data, the study intends to provide insights into the potential of these stem cells in addressing this congenital condition.

Clinical Relevance

The results of this review are designed to provide clinicians with evidence that can help clarify their uncertainties regarding the application of adipocyte stem cells in the treatment of palate and cleft lip. The results are expected to inform clinical decisions, guiding healthcare providers in choosing the most suitable treatment options for their patients.

Materials and Methods

A thorough literature search was performed using PubMed, Medline, and ScienceDirect, covering the period from 2012 to 2022. The keywords employed for the search included "Adipocyte stem cells," "cleft lip treatment," and "cleft palate treatment" (see **Table 1**).

To illustrate the article selection process, a PRISMA flowchart was utilized (**Figure 1**).

Table 1. Criteria for inclusion and exclusion of studies

№	Criteria for inclusion	Criteria for exclusion
1	Randomized controlled trials and case-control studies	Systematic reviews, meta-analyses, expert opinions, or narrative reviews
2	Publications from 2012 to 2022	Publications outside the specified time frame
3	Research involving Adipocyte stem cells	Studies focusing on treatment options other than Adipocyte stem cells
4	Published in English	Publications in languages other than English

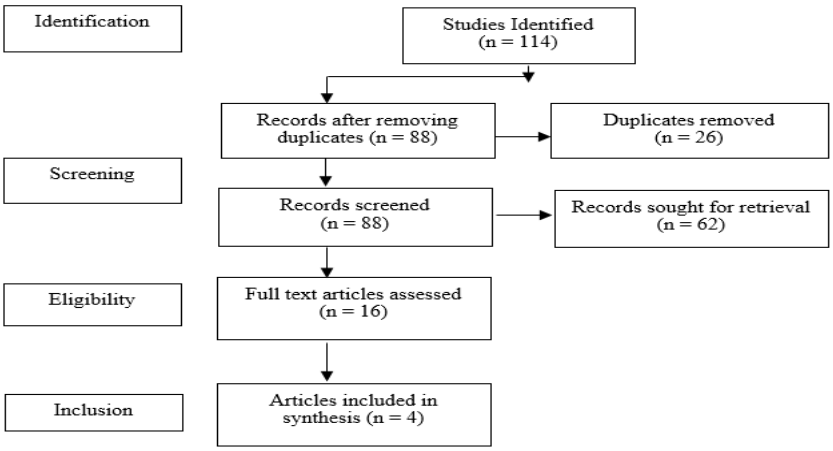

Figure 1. PRISMA flow diagram

Results and Discussion

Risk of bias assessment

All studies were evaluated for quality using the Cochrane risk of bias assessment tool **(Table 2)**.

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 *et al*. [20]	+	+	+	+	+	+	+
Tavakolinejad *et al*. [21]	+	+	+	+	-	+	+
Pourebrahim *et al*. [22]	+	+	+	-	+	+	+
Khojasteh *et al*. [23]	+	-	+	+	+	+	+

The therapeutic potential of adipose tissue-derived mesenchymal stem cells (AT-MSCs) for cleft palate regeneration was evaluated by Alamoudi *et al.* [20]. Radiographic and clinical evaluations at 1.5 and three months post-treatment showed that both AT-MSCs and bone marrow-derived mesenchymal stem cells (BM-MSCs) significantly enhanced bone regeneration, with notable increases in surface area and bone thickness around the damaged area. While BM-MSCs and stem cells from other sources contributed to bone regeneration, AT-MSCs presented several advantages, including lower costs, simpler harvesting procedures, and reduced infection risks.

A study by Tavakolinejad *et al.* [21] investigated the combination of human adipose-derived stem cells (hADSCs), osteogenically differentiated hADSCs, and platelet-rich plasma (PRP) for cleft palate repair. The findings demonstrated a significant reduction in cleft size in the cell-injected group compared to the control group. The cleft area was filled with connective tissue instead of bone, and labeled cells were observed in adjacent tissues, as confirmed by

immunohistochemistry. These results suggest that adipose-derived stem cells and PRP could be a promising approach for cleft palate repair.

Pourebrahim *et al.* [22] compared bone regeneration in cleft palate repair using adipose-derived stem cells versus autogenous bone grafts. Histomorphometric analysis at 15 and 60 days after implantation revealed superior bone regeneration on the autograft side, with 45% and 96% regeneration, respectively, compared to 5% and 70% for the stem cell side.

Khojasteh *et al.* [23] examined the effectiveness of mesenchymal stem cells (BFSCs) harvested from the buccal fat pad for treating cleft deformities. In a randomized study of 10 patients with unilateral anterior maxillary clefts, the treatment groups were divided into three: one group received anterior iliac crest bone and collagen membrane (AIC), another received a lateral ramus cortical plate with BFSCs on natural bovine bone mineral (LRCP+BFSC), and the third received a combination of AIC bone, BFSCs, and collagen membrane (AIC+BFSC). Cone beam computed tomography was used to measure new bone formation 6 months post-treatment. The LRCP+BFSC group showed higher bone production than the AIC group, though the AIC+BFSC group had the highest new bone formation percentage.

This study aimed to evaluate the potential of adipose-derived stem cells (ADSCs) in cleft palate treatment. While the available literature is limited, the data gathered provides valuable insights. ADSCs have shown promising results in the management of cleft palate, aligning with findings by Tobita *et al.* [24], who reported that ADSCs are promising for regenerative medicine applications. These cells can be harvested quickly in huge quantities with minimal donor-site damage. Numerous studies over the past decade have provided preclinical evidence supporting the safety and efficacy of ADSCs for future therapeutic use. However, the efficiency of ADSC harvesting may be influenced by factors such as the donor's age. Wu *et al.* [25] highlighted that ADSCs can be sourced from individuals of all age groups, with infant-derived cells exhibiting better angiogenic and osteogenic capabilities due to longer telomeres. Despite this, osteogenic paracrine effects were similar across all age groups, suggesting that ADSCs remain clinically viable across age ranges from infancy to adulthood.

Adipose-derived stem cells (ADSCs) are integral in tissue regeneration because of their high proliferative capacity in adipose tissue, ability to differentiate into various cell types, secretion of a range of cytokines, and immunomodulatory properties. Numerous clinical trials involving ADSCs have been conducted, with many ongoing, though few phase III studies have been published. ADSCs show promise as a cell source in regenerative medicine, yet further research is needed to establish their safety and the efficacy of using ADSCs in tissue engineering [5].

However, some studies have raised concerns about the potential of human ADSCs to form tumors after prolonged in vitro culture when transplanted into immunodeficient mice. As a result, it is crucial to conduct long-term studies to assess the safety of ADSC transplantation in appropriate host models. Such studies must be designed in collaboration with regulatory bodies to ensure all preclinical concerns are addressed before progressing to phase I clinical trials.

Limitations of the Study

The relatively few relevant studies and the limited information available on ADSCs might not provide sufficient data for dental professionals to confidently select this technique in the planning of regenerative treatments for cleft palate.

Conclusion

While ADSCs have demonstrated promising potential for the reconstruction of cleft palates, the existing evidence is insufficient to support their routine use in clinical practice by oral surgeons.

To establish reliable conclusions on the effectiveness of ADSCs in cleft palate treatment, further clinical trials of higher quality and scale are necessary.

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Conflict of Interest: None

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Ethics Statement: None

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