Review Article

ADIPOCYTE STEM CELLS FOR THE TREATMENT OF CLEFT LIP AND PALATE: A SYSTEMATIC REVIEW

Badr Soliman Alhussain[1], Ahmed Abdullah Bahamid[2], Dhai Taraif Al Turaif[3], Effat Alaa A Alrifae[3], Joud Muhanna Alkahtani[3], Lulwah Mansour Alrejaie[3], Rema Yousef Alomran[3]*

[1]*Department of Restorative Dentistry, PSMMC, Riyadh, Saudi Arabia. bader.hussain@riyadh.edu.sa*
[2]*Department of Preventive Dentistry, Faculty of Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia.*
[3]*Faculty of Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia.*

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ABSTRACT

Adipocyte stem cells (ADSCs) are one type of mesenchymal stem cell derived from adipose tissue. Adipose stem cells are crucial to the creation of new medicines since they have already shown efficacy in the development of new treatments. Many cell types can be formed from this pluripotency, including fat cells (adipogenesis), muscle cells (myogenesis), bones (osteogenesis), and neurons (neurogenesis). Adipose stem cells are crucial to the creation of new medicines since they have already shown efficacy in the development of new treatments. A systematic literature review from 2012 to 2022 was performed using databases such as PubMed, Medline, and ScienceDirect. The keywords used were “Adipocyte stem cells”, “cleft lip treatment”, and “cleft palate treatment”. The limited number of articles included in this study has provided some important information. The use of ADSCs for the management of cleft palate has revealed satisfactory outcomes. Although ADSCs have shown encouraging signs to be used in the reconstruction of cleft palate, the limited amount of evidence is not sufficient in translating it to be practiced regularly by oral surgeons.

Key words: Adipocyte stem cells, Cleft lip, Cleft palate, Systematic review.

Introduction

One of the most frequent craniofacial deformities in neonates is a cleft palate. Deformities of the lip and maxilla, associated with difficulty in speech, eating, and breathing as a result of this hereditary disorder's characteristics, are not only cosmetic but also functional. A cleft is a congenital defect characterized by an abnormal opening in the upper lip, alveolus, or palate. This condition is commonly referred to as harelip. The most appropriate terms are cleft lip, cleft palate, or cleft lip and palate [1, 2].

Many children are born with cleft palate and plate, two of the most common congenital defects that commonly necessitate speech treatment. If the palatal shelves don't fuse entirely, the result is cleft lip and palate. Both the aesthetics and the functionality of this defect are improved as a result of its treatment. Preparation for cleft lip surgery is essential because the surgeon has only one opportunity to do the procedure correctly. Incisions are marked on the skin with ink and the treatment plan is plotted out using the best anthropometric measures [3].

Several causes can lead to the development of a cleft lip and palate (CLP), Cleft lip and palate (CLP), one of the most often occurring congenital abnormalities. It affects the upper jaw and the base of the nose from the time it develops in the womb. Up to one in 500 people in Asian and Native American cultures have CLP. CLP affects one out of every 500 Europeans and one out of every 1,000 African descendants [4].

Adipocyte stem cells (ADSCs) are one type of mesenchymal stem cell derived from adipose tissue. ADSCs can self-renew and specialize into a variety of distinct cell types. There are a variety of mesenchymal stem cells that originate from adipose tissue, including ADSCs. Many cell types can be formed from this pluripotency, including fat cells (adipogenesis), muscle cells (myogenesis), bones (osteogenesis), and neurons (neurogenesis). Adipose stem cells are crucial to the creation of new medicines since they have already shown efficacy in the development of new treatments. Regenerative medicine is a major focus of this study, as well as some of the risks associated with using ADSCs in neoplastic disease [5-7].

A mid-pregnancy anomaly scan, performed between weeks 18 and 21, frequently detects a cleft lip. A cleft palate might be difficult to detect on an ultrasound scan, and this scan will not show all cleft lips [8, 9].

When the structures that make up an infant's upper lip or palate fail to fuse during development in the womb, a cleft lip or palate is the outcome. It is frequently unknown why this occurs in some infants. It's highly unlikely that anything you did or didn't do while pregnant caused this. Cleft lip and palate may be linked to any of the following:

- Child's inherited genetic makeup (although most cases are a one-off).
- Smoking or drinking alcohol during pregnancy.
- Obesity associated with pregnancy.
- A deficiency in prenatal folic acid intake using some anti-seizure drugs and steroid tablets during the first trimester of pregnancy [10, 11].

Cleft palates often need bone transplants utilizing autologous cancellous bone to repair the hard tissue defect. The problem is that these grafts don't fuse with the host bone, thus they eventually collapse. Multipotent cells and biomaterial frameworks are often used in tissue engineering to avoid engraftment challenges. Here, we report the development of cell sheets for the bone healing of cleft palates produced from hMSCs and human stem cells (SHEDs). The ability of hMSCs and SHEDs cell sheets to generate in vitro calcification demonstrated their osteogenic potential [4].

Synergistic increases in ASC yields and decreased production costs should result from the regulation of in vivo niche factors (such as low oxygen content, production of reactive oxygen species, and activation of platelet-derived growth factor receptor signaling). Further, before transplantation, ASCs' regeneration capacity might be increased by preconditioning with these niche elements. The ASC niche is intricate, and there are likely aspects of it that we do not yet fully comprehend [12, 13].

Regenerative medicine cannot function, there is no clinical therapy without stem cells, and stem cells are a primary instrument. As a rule, mesenchymal stem cells (MSCs) produced from bone marrow have a high capacity for bone formation. Stem cells derived from exfoliated deciduous teeth, known as SHED, have also exhibited a remarkable capacity for osteogenic development. SHED cells can mend a critical-sized lesion in the calvarium of a mouse by their osteogenic differentiation potential [14, 15].

Dental and nondental mesenchymal stem cells have been used to regenerate the maxilla and mandibles. These cells have been used to regenerate tooth pulp, periodontal ligaments, enamel and dentin, salivary glands, cleft lips and palates, and the craniofacial region. This is a fresh idea that should be tested to improve research in the field of oral mucosal disease treatment using stem cells [16-19].

Study hypotheses
Adipocyte stem cells provide high-quality treatment for cleft lip and palate patients.

PICO question
Participants: Cleft lip and palate patients
Intervention: Adipocyte stem cells
Control: Treatment options other than adipocyte stem cells
Outcome: Treatment of cleft lip and palate

Aims of the study
The purpose of this systematic review was to determine the efficacy and success rate of adipocyte stem cells in the treatment of cleft lip and palate.

Clinical applications
The findings of this systematic study will help clinical practitioners to confirm their doubts about the use of adipocyte stem cells in the treatment of cleft lip and palate.

Materials and Methods

We used PubMed, Medline, and Science Direct, to conduct a comprehensive literature search covering the years 2012–2022. The keywords used were “Adipocyte stem cells”, “cleft lip treatment”, and “cleft palate treatment” **(Table 1)**. PRISMA flowchart was used to describe the selection process of searched articles **(Figure 1)**.

Table 1. Inclusion and exclusion criteria

№	Inclusion criteria	Exclusion criteria
1.	Controlled trials and case-control studies	Systematic reviews or meta-analyses or expert opinions or narrative reviews
2.	Published between 2012 and 2022	Not within the given time period
3.	Studies including Adipocyte stem cells	Studies with treatment options other than Adipocyte stem cells
4.	English language of publication	Language other than English

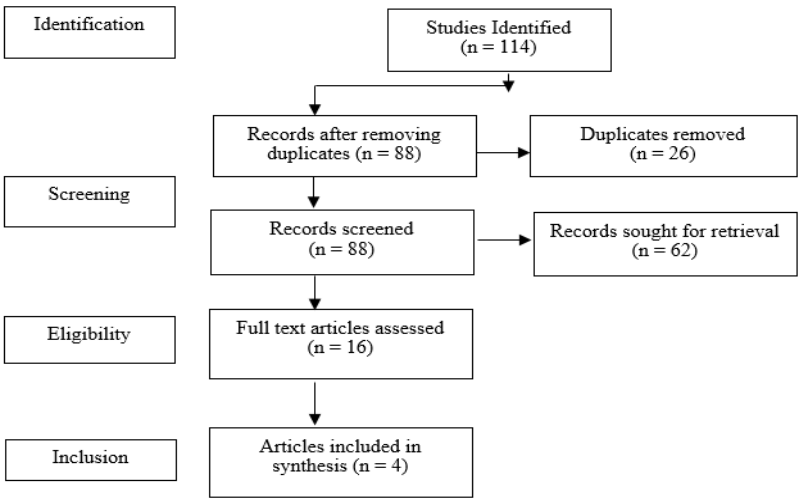

Figure 1. PRISMA Flow Diagram

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*., 2019 [20]	+	+	+	+	+	+	+
Tavakolinejad *et al*., 2014 [21]	+	+	+	+	-	+	+
Pourebrahim *et al*., 2013 [22]	+	+	+	-	+	+	+
Khojasteh *et al*., 2017 [23]	+	-	+	+	+	+	+

Results and Discussion

The therapeutic potential for cleft palate regeneration using adipose tissue-derived mesenchymal stem cells (ATMSCs) was evaluated by Alamoudi *et al*. (2019) [20]. After 1.5 and 3 months, the bone repair was evaluated radiographically and clinically. In this study, we found that both types of stem cells (AT-MSCs and BM-MSCs) significantly improved bone repair and regeneration by increasing bone thickness and surface area around the damaged area. Bone marrow-derived MSCs and MSCs from other sources were useful in regenerating bone. There are several advantages to using AT-MSCs over BM-MSCs, including a lower price tag, easier harvesting, a safer method to get stem cells, and a lower chance of infection.

Human Adipose-derived stem cells (hADSCs) and osteogenically differentiated hADSCs were combined with platelet-rich plasma (PRP) to heal cleft palates in a study published by Tavakolinejad *et al*., 2014. The results showed a significant difference in cleft size between cell-injected and control groups, with the cleft area filling with connective tissue rather than osseous tissue. Labeled cells were also seen in adjacent tissue, as shown by the immunohistochemistry results. The results of this study showed promise for the use of adipose-derived stem cells and PRP in CP repair.

Khojasteh *et al*. (2017) studied the effectiveness of a lateral ramus cortical plate containing mesenchymal stem cells (BFSCs) harvested from a buccal fat pad in treating human cleft deformity [23]. Ten individuals with unilateral anterior maxillary clefts were randomly divided into three groups. The first group received treatment with bone from the anterior iliac crest (AIC) and a collagen membrane (AIC group), and the second group received a bone plate from the lateral ramus cortical bone (LRCP) that had BFSCs mounted on a natural bovine bone mineral (LRCP+BFSC). The third group received AIC bone, BFSCs cultured on natural bovine bone minerals, and a collagen membrane (AIC+BFSC). Cone beam computed tomography measured the amount of new bone formed 6

months after the treatment. The percentage of new bone production in the AIC group was the lowest. Defects were closed, and new bone formation (in %) was higher in the LRCP+BFSC group but to a lesser extent than in the AIC+BFSC group.

Pourebrahim *et al*., (2013) compared bone regeneration of cleft palate from adipose-derived stem cells and autogenous bone graft [22]. Histomorphometry was used to measure bone regeneration at 15 and 60 days after implantation. The data were analyzed using descriptive statistics, and t-tests were used to analyze the data. Bone regeneration on the autograft side was higher than on the stem cell side at 45% and 96%, respectively, compared to 5% and 70%.

The purpose of this research was to assess how useful adipose-derived stem cells are. for the treatment of cleft palate. It can be noted from the findings that the amount of information on this material and relative treatment was not ample. However, the limited number of articles included in this study has provided some important information. The use of ADSCs for the management of cleft palate has revealed satisfactory outcomes. This is supported by Tobita *et al*., (2011) as they reported ADSCs being encouraging in the field of regenerative medicine [24]. These cells may be collected rapidly in large quantities with little donor-site damage. Several pieces of research over the last decade have provided preclinical evidence on the efficiency and safety of adipose-derived stem cells, supporting their usage in upcoming therapeutic uses. However, it is worth noting that the harvesting of ADSCs is dependent on factors such as aging. Wu *et al*., (2013) documented that ADSCs are obtainable from all age groups [25]. Infant-derived cells are anatomically spindle-shaped, with extended telomeres, and revealed improved angiogenic and osteogenic competencies compared with older cells. On the other hand, all age groups displayed identical osteogenic paracrine action, and the authors postulate that clinical applicability is well-maintained in the age of the adult to elderly period.

Adipogenic stem cells (ADSCs) play a significant role in tissue rejuvenation due to their high cell output in adipose tissue, ability to segregate into various lineages, secretion of many cytokines, and immunomodulatory effects. A handsome number of clinical trials consuming ADSCs have previously been performed and several of them are currently going on. Yet, very few phase III clinical investigations have been published. ADSCs are an encouraging cell source for regenerative medicine, and more study is required to warrant the safety of ADSCs and the effectiveness of tissue engineering using ADSCs [5].

On the other hand, a few investigations have claimed that human ADSCs, after extended culture in vitro, possess the capacity of forming tumors in immunodeficient mice. Therefore, long-term experiments exploring the safety of ADSC transplantation in suitable host models will be obligatory. Such trials should be planned in consultation with regulatory agencies to assure that all preclinical queries are addressed before progressing to phase I studies in patients.

Limitations of the study

A small number of relevant articles as well as limited information about ADSCs may not be sufficient for dental practitioners to choose this technique when planning a regenerative treatment for cleft palate.

Conclusion

- Although ADSCs have shown encouraging signs to be used in the reconstruction of cleft palate, the limited amount of evidence is not sufficient in translating it to be practiced regularly by oral surgeons.
- There is a need of conducting further higher levels of clinical trials which can give us reliable evidence regarding the use of ADSCs in cleft palate management.

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Conflict of interest: None

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Ethics statement: This study fulfills the ethical requirements of Riyadh Elm University.

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