

Use of stem cells from deciduous teeth in bone regeneration for the treatment of cleft lip and palate: A review of *in vivo* studies

Uso de células-tronco de dentes decíduos na regeneração óssea para tratamento de fissura labiopalatina: Revisão de estudos in vivo

Luana Souza da Silva¹

Ana Clara Araújo Miranda Santos¹

Cesar Augusto Casotti³

Marcelo Fabiano Gomes Borriolo⁴

Mateus Cardoso Oliveira^{2,3}

Resumo

Objective: This study aimed to review *in vivo* studies on the use of stem cells derived from exfoliated deciduous teeth (SHED) for bone regeneration, particularly in the treatment of cleft lip and/or palate (CL/P). **Methodology:** The review followed PRISMA guidelines and included studies from PubMed, Scopus, and Google Scholar databases, published in the last 10 years in English, Spanish, or Portuguese. Strict inclusion and exclusion criteria were applied, focusing on *in vivo* studies using SHED for CL/P treatment. Keywords such as "Bone Regeneration," "Tissue Engineering," and "SHED" were used for the search. After screening 1,045 records and excluding duplicates, 7 studies were selected for full review. **Results:** The review identified 7 relevant studies, 6 of which were *in vivo* animal studies, and 1 was a clinical case report. These studies demonstrated that SHEDs effectively promoted bone regeneration, presenting a less invasive and promising alternative to traditional bone grafting techniques. **Conclusion:** SHEDs show significant potential in bone regeneration, offering a less invasive treatment option with fewer complications compared to autogenous bone grafts. However, more research is needed to address long-term safety, tumorigenesis, and optimal clinical applications before widespread clinical adoption.

Keywords: Cleft Palate; Stem Cell Research; Bone Regeneration; Bone Graft

<http://dx.doi.org/10.5335/rfo.v30i1.16372>

1- Undergraduate Student, Department of Dentistry, Mauricio de Nassau University Center - UNINASSAU, Vitória da Conquista – BA – Brazil

2- Professor, Department of Dentistry, Mauricio de Nassau University Center - UNINASSAU, Vitória da Conquista – BA – Brazil

3- Professor, Graduate Program in Nursing and Health, State University of Southwest Bahia – UESB, Jequié – BA – Brazil

4- Professor, Department of Oral Diagnosis, Piracicaba Dental School – FOP-UNICAMP, Piracicaba – SP – Brazil

Introduction

Cleft lip, with or without cleft palate (CL/P), is widely recognized as the most common congenital craniofacial defect, resulting from the incomplete development of facial and oral tissues during the embryonic phase¹. Individuals affected by CL/P often experience speech difficulties, dental anomalies, hearing problems, facial deformities, and chronic ear infections². In addition to physical complications that compromise quality of life over time, CL/P is also associated with psychosocial challenges, such as low self-esteem³.

Conventional treatment for CL/P generally involves secondary bone grafting using autogenous bone harvested from the iliac crest, aiming to form a bone bridge for the creation of the alveolar ridge and closure of the oronasal fistula^{4,5}. However, this approach presents several limitations, including complications such as bleeding, nerve injuries, aesthetic problems, pain, infection, and functional tissue loss⁶⁻⁸.

Although autogenous grafts are effective, they often result in donor site morbidity and prolonged recovery times, which can negatively impact patients' quality of life⁹. Furthermore, bone grafts using autologous cancellous bone may face difficulties in fully integrating with the recipient bone and are subject to resorption¹⁰. Due to these limitations, less invasive methods that could replace bone grafting and promote tissue regeneration have been extensively investigated.

Stem cells stand out due to their unique properties¹¹, particularly their ability to remain undifferentiated, combined with their capacity for proliferation and self-renewal¹². Mesenchymal stem cells (MSCs) can be extracted from various sources, such as adipose tissue, bone marrow, and dental pulp¹³. Stem cells derived from human exfoliated deciduous teeth (SHED) represent a population of stem cells with postnatal characteristics that allow for extensive proliferation and multipotential differentiation¹⁴. Moreover, these cells present a low risk of oncogenesis and have a high proliferative capacity, being able to differentiate into various cell types such as neurons, adipocytes, and odontoblasts¹⁴. *In vivo* studies have demonstrated that SHEDs are effective in inducing bone formation, dentin production, and the expression of neuronal markers¹⁵. In addition to being derived from a highly accessible tissue, these cells can provide sufficient quantities for clinical applications, cell transplantation, and tissue engineering¹⁴.

For these reasons, deciduous teeth have emerged as an ideal source of stem cells for the repair of damaged dental structures, induction of bone regeneration, and potential treatment of neural tissue injuries or degenerative diseases, due to their greater accessibility^{14,15}.

In this context, one of the conditions that could benefit from the use of SHEDs in tissue engineering is cleft lip and palate. Therefore, the objective of this study is to present a review of *in vivo* studies that used SHED for bone regeneration, focusing on the treatment of patients with cleft lip and palate.

Materials and methods

The study was conducted in accordance with the PRISMA flowchart guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). One researcher conducted the data collection and analysis on the therapeutic potential of stem cells derived from exfoliated deciduous teeth (SHED) in regenerative medicine for patients with cleft lip and palate. Following strict inclusion and exclusion criteria, various online databases such as PubMed, Scopus, and Google Scholar were consulted. Relevant studies were identified through a search using various combinations of keywords, such as “Bone Regeneration,” “Tissue Engineering,” “Mesenchymal Stem Cell Transplantation,” “SHED,” “Human Exfoliated Deciduous Teeth Stem Cells,” “Mesenchymal Stem Cells,” “Deciduous Teeth,” “Dental Stem Cells,” “Progenitor Cells,” “Cleft Lip,” “Cleft Palate,” “Alveolar Cleft,” “Rats,” “Animal Model,” “Wistar,” “Mice,” and “Clinical Trials.” For the screening and selection of records, the Rayyan application was used.

Predefined inclusion criteria encompassed full-text studies, either open access or subscription-based, published within the last 10 years in English, Spanish, or Portuguese, which investigated the use of SHED in research related to regenerative medicine in patients with cleft lip and palate, focusing on *in vivo* studies.

Exclusion criteria included posters, preprints, reviews, studies that used other types of stem cells, *in vitro* research, studies that did not address the therapeutic potential of SHED in cleft lip and palate, research involving SHED in other pathologies or anomalies, editorial or opinion articles, inadequately documented treatments, or studies that presented a risk of bias according to established criteria, as well as duplicate studies.

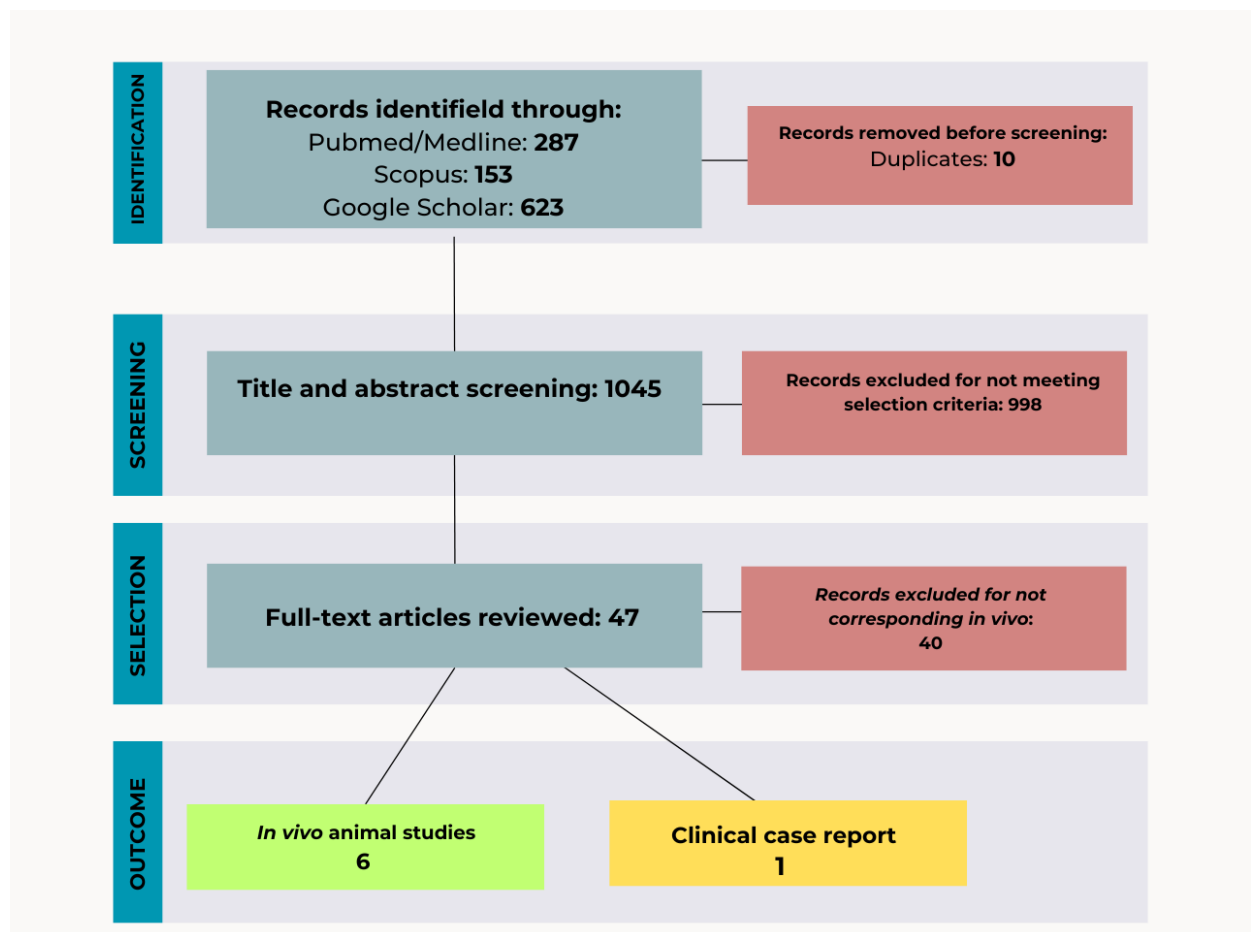
The researcher followed a sequence of steps for data extraction as suggested by Souza, Silva, and Carvalho, 2010¹⁶, which included: 1) formulating the guiding question; 2) conducting the literature search; 3) selecting relevant studies; 4) critically analyzing the selected studies; 5) discussing the findings; and 6) presenting the integrative review.

The selection process began with the removal of duplicate records, followed by reading titles and abstracts, and subsequently the full-text reading and evaluation of the eligibility of articles according to the proposed research theme, aiming to answer the guiding question in line with the previously established inclusion and exclusion criteria.

Results

To conduct a review of *in vivo* studies that used SHED for bone regeneration, with an emphasis on the treatment of patients with cleft lip and palate over the past 10 years, this research identified 1,063 records, with 287 from the PubMed/Medline database, 153 from Scopus, and 623 from Google Scholar. After removing 18 duplicate articles, 1,045 records remained for title and abstract screening. At this stage, 998 studies were excluded for addressing other types of stem cells or not exploring the therapeutic potential of SHED in patients with cleft lip and palate, resulting in 47 articles for full-text review. Of these, 40 were eliminated for not corresponding to *in vivo* research. Finally, 7 articles were selected for review and classified according to the theme addressed: *in vivo* animal research (6 records) and a clinical case report (1) (Figure 1).

Figure 1 - Flowchart of sample constitution



Discussion

Patients who do not receive adequate treatment for cleft lip and/or palate (CL/P) face a range of significant complications, such as otitis media with effusion^{17,18}, speech difficulties¹⁸, and malocclusion resulting from the loss of labial pressure¹⁹. The absence of therapeutic intervention for CL/P can profoundly impact the quality of life of affected individuals, affecting not only physical aspects but also psychological and social dimensions²⁰.

Before advances in regenerative medicine, the primary technique for CL/P reconstruction was bone grafting from the iliac crest, which is still considered the gold standard²⁰. However, other sources of autografts, such as ribs, cranial vault, and tibia, have also been employed^{22,23}. Although autografts present relevant clinical advantages, such as greater stability and bone integration, they also come with significant disadvantages that drive the search for less invasive and more conservative methods for palatal reconstruction²⁴. For instance, oronasal fistulas are

common postoperative complications in cleft palate surgeries, closely related to the surgical technique and tissue management²⁵. Additional complications, including paresthesia, pain, functional impairment at the donor site, bone resorption, the need for multiple interventions, and prolonged surgical time, further reinforce the need to explore new therapeutic approaches²⁶⁻²⁸. In this context, regenerative methods have gained prominence as they are less dependent on surgical technique and applicable to a wide range of orofacial conditions^{29,30}.

Tissue engineering, which relies on biomaterials to restore both tissue morphology and function, has brought significant advancements in bone regeneration, particularly through the use of 3D biomimetic scaffolds produced using various materials and methods, offering new alternatives for CL/P treatment³¹. These scaffolds provide physical structures that facilitate osteoblast attachment and proliferation—crucial elements for effective bone regeneration³². Biomaterials used in these scaffolds can be of natural or synthetic origin, with properties enhancing osteoinduction and osteoconduction³². Specific biomaterial compounds, such as bioceramics, demineralized bone matrices, bioactive glasses, and composite materials combined with bioactive inorganic substances, have shown particular promise for CL/P treatment due to their biological properties, including osteoconduction, biocompatibility, chemical similarity to natural bone, and promotion of osteoblast proliferation and differentiation³³.

Despite progress, the complexity of the tissues and structures involved in CL/P, coupled with the need for functional reconstruction of highly vascularized bones, such as in the craniofacial region, continues to pose significant challenges in tissue engineering. The creation of a well-organized hierarchical vascular network is essential for the success of these interventions^{34,35}. Consequently, more research is required to overcome these challenges and facilitate complete, organized, and successful tissue regeneration.

The use of stem cells in regenerative medicine, especially for CL/P treatment, is emerging as a promising alternative to traditional surgical interventions³⁶. In particular, mesenchymal stem cells (MSCs), with their potential to differentiate into various tissue types, are ideal for reconstructive procedures in CL/P cases³⁷. The co-culture of these cells with scaffolds can optimize the regenerative process, offering a dual approach in tissue engineering³⁸.

Recent advancements in tissue engineering for replacing lost or damaged tissues have driven the use of human stem cells in conjunction with biomaterial supports³⁹. Among these, stem cells derived from human exfoliated deciduous teeth (SHED) have emerged as promising candidates for bone regeneration due to their ability to differentiate into osteoblasts⁴⁰. In addition to their differentiation capabilities, SHEDs promote bone healing through paracrine mechanisms, influencing adjacent cells to participate in the regenerative process⁴⁰.

Various methods have been applied in both *in vivo* and clinical studies with SHEDs. One study investigated the effect of SHED transplantation after inducing a bone defect in the mandible of dogs⁴¹. After 12 weeks, new bone formation was observed in both the lingual region and the floor of the defect, areas where compact bone existed⁴¹. Another study demonstrated that SHEDs serve as an effective cellular resource for repairing maxillary alveolar defects in rats, presenting a promising model for defect reconstruction in CL/P patients⁴². Nakajima et al. (2018) investigated bone regeneration following SHED application, comparing them with human dental pulp stem cells (hDPSCs) and human bone marrow mesenchymal stem cells (hBMSCs) in an *in vivo* experiment conducted after creating a bone defect in the calvaria of immunodeficient mice⁴³. The results indicated that the transplantation of SHEDs and hDPSCs induced bone formation in amounts comparable to those observed after hBMSC transplantation⁴³.

In 2019, two additional studies were reported. One produced and evaluated cell sheets (CSs) for cleft palate bone repair derived from human mesenchymal stem cells (hMSCs) and SHEDs, both sources of osteogenic cells⁴⁴. The authors observed that these CSs promoted *in vitro* calcification, demonstrating the osteogenic potential of the cells, in addition to expressing specific osteogenic markers such as Osterix (OSX), Osteocalcin (OCN), and Osteopontin (OPN) after insertion into *ex vivo* and *in vivo* cultured embryonic palatal shelves⁴⁴. Another study by Prahasanti et al. analyzed the expression of the biomarkers Osteoprotegerin (OPG) and receptor activator of NF- κ B ligand (RANKL) after the application of a hydroxyapatite scaffold combined with SHEDs to correct alveolar bone defects³⁹. The *in vivo* analysis indicated that the hydroxyapatite scaffold combined with SHEDs promoted an increase in OPG and a reduction in RANKL expression, demonstrating the great potential of this biomaterial in alveolar bone defect regeneration³⁹. OPG

plays a crucial role in protecting the skeleton against excessive bone resorption by binding to RANKL and preventing its interaction with the RANK receptor³⁹.

In 2020, another study evaluated the bone regenerative effects of SHEDs and conditioned medium (CM)—paracrine factors secreted by MSCs during cell culture with wound-healing potential⁴⁵. In this study, bone defects were created in the calvaria of immunodeficient mice, and stem cells or SHED-CM were implanted⁴⁵. Bone regeneration was more pronounced in defects treated with stem cells and CM compared to controls. Therefore, SHED-CM proved to be more effective for alveolar cleft reconstruction in patients, promoting bone regeneration in a less invasive manner⁴⁵.

An important milestone in the clinical application of tissue engineering with stem cells occurred in 2020, when Tanikawa et al. conducted the first clinical report using deciduous dental pulp stem cells (DDPSC) in children for alveolar bone defect regeneration⁴⁶. In this study, DDPSCs were combined with a hydroxyapatite-collagen sponge (Bio-Oss Collagen® 250 mg, Geistlich) to repair defects during tooth eruption⁴⁶. The cells were individually isolated from each patient and combined with the biomaterial, then used to fill the alveolar defect⁴⁶. The results were evaluated by cone-beam computed tomography at six and twelve months post-procedure⁴⁶. The researchers observed progressive alveolar bone union in all patients, highlighting that DDPSC therapy resulted in adequate healing of alveolar defects, with excellent viability and safety⁴⁶. Additionally, studies indicate that using DDPSCs combined with biomaterials can effectively close alveolar defects, achieving 75.6% bone fill six months postoperatively⁴⁶. The application of DDPSCs proved advantageous compared to traditional iliac crest grafting, presenting fewer complications and no reports of significant donor site pain⁴⁶.

Stem cell therapies for cleft lip and palate (CL/P) have shown considerable potential to improve surgical outcomes and open new treatment possibilities. However, this field is still emerging, and more research is needed to optimize various parameters, such as identifying the most effective stem cell types and determining ideal dosages for CL/P treatment⁴⁷. Additionally, despite advancements, significant challenges remain, including the risk of tumor formation and immune rejection, which are important barriers to the clinical application of these therapies⁴⁸.

Although the potential of stem cell therapies for CL/P is promising, the complexities involved—particularly regarding safety, efficacy, and outcome assessment—underline the need for ongoing research and clinical trials. This effort is essential to ensure that the application of these therapies is not only effective but also safe for patients, enabling their integration into clinical practice in a responsible and ethical manner.

Conclusion

Based on the review of *in vivo* studies on the use of stem cells derived from exfoliated deciduous teeth (SHED) in bone regeneration for the treatment of cleft lip and palate, it is concluded that these cells represent a promising alternative to traditional bone grafting methods. The studies analyzed demonstrated that SHEDs have the ability to effectively promote bone formation with a lower risk of complications and less invasiveness compared to autogenous grafts. However, for this approach to be safely and effectively integrated into clinical practice, further research is needed to address critical issues such as long-term safety, tumor formation potential, optimal dosages, and the patient's immune response. Additionally, transitioning to clinical practice will require the standardization of treatment protocols and the conduction of robust clinical trials to validate the efficacy and safety of these therapies on a larger scale.

Abstract

Objective: This study aimed to review *in vivo* studies on the use of stem cells derived from exfoliated deciduous teeth (SHED) for bone regeneration, particularly in the treatment of cleft lip and/or palate (CL/P). **Methodology:** The review followed PRISMA guidelines and included studies from PubMed, Scopus, and Google Scholar databases, published in the last 10 years in English, Spanish, or Portuguese. Strict inclusion and exclusion criteria were applied, focusing on *in vivo* studies using SHED for CL/P treatment. Keywords such as “Bone Regeneration,” “Tissue Engineering,” and “SHED” were used for the search. After screening 1,045 records and excluding duplicates, 7 studies were selected for full review. **Results:** The review identified 7 relevant studies, 6 of which were *in vivo* animal studies, and 1 was a clinical case report. These studies demonstrated that SHEDs effectively promoted bone regeneration, presenting a less invasive and promising alternative to traditional bone grafting techniques. **Conclusion:** SHEDs show significant potential in bone regeneration, offering a less invasive treatment option with fewer complications compared to autogenous bone grafts. However, more research is needed to address long-term safety, tumorigenesis, and optimal clinical applications before widespread clinical adoption.

References

- Heydari MH, Sadeghian A, Khadivi G, Mustafa HJ, Javinani A, Nadjmi N, Khojasteh A. Prevalence, trend, and associated risk factors for cleft lip with/without cleft palate: a national study on live births from 2016 to 2021. *BMC Oral Health*. 2024;24(1):36. doi: 10.1186/s12903-023-03797-z.
- Mitchell JC, Wood RJ. Manejo da fissura labiopalatina na atenção primária. *J Pediatr Health Care*. 2000;14(1):13-9. doi: 10.1016/S0891-5245(00)70039-3.
- Balasubramaniyan S, Raghunathan V, Rajashekhar B, Sathiyasekaran BWC, Nagarajan R. Planning community-based intervention for speech for children with cleft lip and palate from rural South India: a needs assessment. *Indian J Plast Surg*. 2017;50(3):295-301. doi: 10.4103/ijps.IJPS_174_17.
- Fu ML, Aldosari M, Chakraborty A, Ko J, Tahir P, Oberoi S. The effects of presurgical orthodontic treatment on the outcome of secondary bone graft for individuals with cleft lip and palate. *J Craniofac Surg*. 2024; Advance online publication. doi: 10.1097/SCS.00000000000010431.
- Haj M, Hakkesteeft SN, Poldermans HG, de Gier HHW, Versnel SL, Wolvius EB. Speech outcomes after delayed hard palate closure and synchronous secondary alveolar bone grafting in patients with cleft lip, alveolus and palate. *Arch Plast Surg*. 2024;51(4):378-85. doi: 10.1055/s-0044-1787002.
- Joshi KR, Das G, Shrestha A, Khanal LR, Guragain M. Management of cleft palate in middle schooler: a case report. *J Nepal Prosthodont Soc*. 2023;6(1):36-9.
- Dhooghe N, Verhelst P, Vandenbosch K, Engelen B, Vanderhaeghe F, Nagy K, Vanenbosch K. Chirurgische behandeling lip-en verhemeltespleet. *Tijdschr Geneeskde Gezondhzorg*. 2023;6.
- Ahmed O, Yasmeen S, Khan MI, Beg MSA. A novel technique for prevention of anterior fistula and facilitation of alveolar cleft repair: gingivoperiosteoplasty with palatoplasty. *Pak J Med Sci*. 2022;38(7):1816-20. doi: 10.12669/pjms.38.7.542.
- Singh GP, Vohra G. A novel modification of nasoalveolar molding procedure to enhance ease of use. *J Cleft Lip Palate Craniofac Anomal*. 2023;10(1):40-4.
- Lee JM, Kim HY, Park JS, Lee DJ, Zhang S, Green DW, Jung HS. Developing palatal bone using human mesenchymal stem cell and stem cells from exfoliated deciduous teeth cell sheets. *J Tissue Eng Regen Med*. 2019;13(2):319-27. doi: 10.1002/term.2811.
- Tian Z, Yu T, Liu J, Wang T, Higuchi A. Introduction to stem cells. *Prog Mol Biol Transl Sci*. 2023;199:3-32. doi: 10.1016/bs.pmbts.2023.02.012.
- Anggraeni R, Ana ID. Stem cells: basic understanding and its relevance to regenerative mechanism. 2024.
- Zhu X, Xu X, Shen M, Wang Y, Zheng T, Li H, et al. Transcriptomic heterogeneity of human mesenchymal stem cells derived from bone marrow, dental pulp, adipose tissue, and umbilical cord. *Cell Reprogram*. 2023;25(4):162-70. doi: 10.1089/cell.2023.0019.
- Mohd Nor NH, Mansor NI, Mohd Kashim MIA, Mokhtar MH, Mohd Hatta FA. From teeth to therapy: a review of therapeutic potential within the secretome of stem cells from human exfoliated deciduous teeth. *Int J Mol Sci*. 2023;24(14):11763. doi: 10.3390/ijms241411763.
- Fracaro L, Hochuli AHD, Selenko AH, Capriglione LGA, Brofman PRS, Senegaglia AC. Mesenchymal stromal cells derived from exfoliated deciduous teeth express neuronal markers before differentiation induction. *J Appl Oral Sci*. 2023;31:e20220489. doi: 10.1590/1678-7757-2022-0489.
- Souza MT, Silva MD, Carvalho R. Integrative review: what is it? How to do it? Einstein (Sao Paulo). 2010;8(1):102-6. doi: 10.1590/S1679-45082010RW1134.
- Linkugel AD, Trivedi PB, Varagur K, Skolnick GB, Menezes MD, Dunskey KA, et al. Multidisciplinary optimal outcomes reporting and team clinic retention in isolated nonsyndromic cleft palate. *Cleft Palate Craniofac J*. 2023; Advance online publication. doi: 10.1177/10556656231205974.
- Yohana N, Handoko H. Understanding of speech production in cleft lip/palate: a review. *J Arbitrer*. 2023;10(4):437-46.
- Sischo L, Wilson-Genderson M, Broder HL. Quality-of-life in children with orofacial clefts and caregiver well-being. *J Dent Res*. 2017;96(13):1474-81. doi: 10.1177/0022034517725707.
- Yusof MS, Mohd Ibrahim H. The impact of cleft lip and palate on the quality of life of young children: a scoping review. *Med J Malaysia*. 2023;78(2):250-8.

21. Park JJ, Rochlin DH, Parsaei Y, Shetye PR, Witek L, Leucht P, et al. Bone tissue engineering strategies for alveolar cleft: review of preclinical results and guidelines for future studies. *Cleft Palate Craniofac J*. 2023;60(11):1450-61. doi: 10.1177/10556656221104954.
22. Brudnicki A, Petrova T, Dubovska I, Kuijpers-Jagtman AM, Ren Y, Fudalej PS. Alveolar bone grafting in unilateral cleft lip and palate: impact of timing on palatal shape. *J Clin Med*. 2023;12(24):7519. doi: 10.3390/jcm12247519.
23. Nagatsuka T, Matsuura N, Ntege EH, Shimizu Y. Autologous rib cartilage reconstruction after silicone implant removal in a patient with bilateral cleft lip and palate: a case report. *Cureus*. 2024;16(4):e58452. doi: 10.7759/cureus.58452.
24. Tavelli L, Barootchi S, Stefanini M, Zucchelli G, Giannobile WV, Wang HL. Wound healing dynamics, morbidity, and complications of palatal soft-tissue harvesting. *Periodontol 2000*. 2023;92(1):90-119. doi: 10.1111/prd.12466.
25. Miranda BL, Júnior JLA, Paiva MAF, Lacerda RHW, Vieira AR. Management of oronasal fistulas in patients with cleft lip and palate. *J Craniofac Surg*. 2020;31(6):1526-8. doi: 10.1097/SCS.00000000000006213.
26. Parvini P, Obreja K, Sader R, Becker J, Schwarz F, Salti L. Surgical options in oroantral fistula management: a narrative review. *Int J Implant Dent*. 2018;4(1):40. doi: 10.1186/s40729-018-0152-4.
27. Scattarella A, Ballini A, Grassi FR, Carbonara A, Ciccolella F, Dituri A, et al. Treatment of oroantral fistula with autologous bone graft and application of a non-reabsorbable membrane. *Int J Med Sci*. 2010;7(5):267-71. doi: 10.7150/ijms.7.267.
28. Park WB, Bae MS, Park W, Lim HC, Han JY. A novel approach for the treatment of recurrent oroantral fistula occurring at an infected sinus augmentation site. *Medicina (Kaunas)*. 2024;60(2):343. doi: 10.3390/medicina60020343.
29. Francisco I, Paula AB, Oliveiros B, Fernandes MH, Carrilho E, Marto CM, Vale F. Regenerative strategies in cleft palate: an umbrella review. *Bioengineering (Basel)*. 2021;8(6):76. doi: 10.3390/bioengineering8060076.
30. Ahn G, Lee JS, Yun WS, Shim JH, Lee UL. Cleft alveolus reconstruction using a three-dimensional printed bioresorbable scaffold with human bone marrow cells. *J Craniofac Surg*. 2018;29(7):1880-3. doi: 10.1097/SCS.00000000000004747.
31. Xu H, Zhang Y, Zhang Y, Zhao Z, Xue T, Wang J, Ding Y. 3D bioprinting advanced biomaterials for craniofacial and dental tissue engineering—A review. *Mater Des*. 2024;112886.
32. Ali YH, El-Shazly M, Taha A, Ali T, Bakri S. Tissue engineering strategies in cleft palate. In: *Surgical Atlas of Cleft Palate and Palatal Fistulae*. Singapore: Springer Singapore; 2022. p. 1-10.
33. Taori T, Borle A, Maheshwari S, Reche A. An insight into the biomaterials used in craniofacial tissue engineering inclusive of regenerative dentistry. *AIMS Bioeng*. 2023;10(2).
34. Yang F, Garg A, Clark S, Dikyol C, Feinberg A, Ozdoganlar B, LeDuc PR. 3D freeform ice printing for fabricating biomimetic vascular networks in engineered tissue. *Biophys J*. 2024;123(3):436a.
35. Shahbazi A, Mueller AA, Mezey S, Gschwindt S, Kiss T, Baksa G, Kisnisci RS. Is the collateral circulation pattern in the hard palate affected by cleft deformity? *Clin Oral Investig*. 2024;28(5):277. doi: 10.1007/s00784-024-05627-0.
36. Mazzetti MPV, Alonso N, Brock RS, Ayoub A, Massumoto SM, Eça LP. Importance of stem cell transplantation in cleft lip and palate surgical treatment protocol. *J Craniofac Surg*. 2018;29(6):1445-51. doi: 10.1097/SCS.00000000000004766.
37. Kanwal L, Khawaja M, Idrees W, Sukhia RH, Fida M. The implication of stem cell therapy in cleft lip and palate and other craniofacial anomalies—a literature review. *J Calif Dent Assoc*. 2023;51(1):2246192.
38. Amiri MA, Lavaee F, Danesteh H. Use of stem cells in bone regeneration in cleft palate patients: review and recommendations. *J Korean Assoc Oral Maxillofac Surg*. 2022;48(2):71-8. doi: 10.5125/jkaoms.2022.48.2.71.
39. Prahasanti C, Subrata LH, Saskianti T, Suardita K, Ernawati DS. Combined hydroxyapatite scaffold and stem cell from human exfoliated deciduous teeth modulating alveolar bone regeneration via regulating receptor activator of nuclear factor- κ B and osteoprotegerin system. *Iran J Med Sci*. 2019;44(5):415-21.

40. Zhang N, Xu L, Song H, Bu C, Kang J, Zhang C, et al. Tracking of stem cells from human exfoliated deciduous teeth labeled with Molday ION Rhodamine-B during periodontal bone regeneration in rats. *Int J Stem Cells*. 2023;16(1):93-107. doi: 10.15283/ijsc.21204.
41. Behnia A, Haghighat A, Talebi A, Nourbakhsh N, Heidari F. Transplantation of stem cells from human exfoliated deciduous teeth for bone regeneration in the dog mandibular defect. *World J Stem Cells*. 2014;6(4):505-10. doi: 10.4252/wjsc.v6.i4.505.
42. Jahanbin A, Rashed R, Alamdari DH, Koohestanian N, Ezzati A, Kazemian M, et al. Success of maxillary alveolar defect repair in rats using osteoblast-differentiated human deciduous dental pulp stem cells. *J Oral Maxillofac Surg*. 2016;74(4):829.e1-829.e9. doi: 10.1016/j.joms.2015.11.033.
43. Nakajima K, Kunimatsu R, Ando K, Ando T, Hayashi Y, Kihara T, et al. Comparison of the bone regeneration ability between stem cells from human exfoliated deciduous teeth, human dental pulp stem cells and human bone marrow mesenchymal stem cells. *Biochem Biophys Res Commun*. 2018;497(3):876-82. doi: 10.1016/j.bbrc.2018.02.156.
44. Hiraki T, Kunimatsu R, Nakajima K, Abe T, Yamada S, Rikitake K, Tanimoto K. Stem cell-derived conditioned media from human exfoliated deciduous teeth promote bone regeneration. *Oral Dis*. 2020;26(2):381-90. doi: 10.1111/odi.13244.
45. Tanikawa DYS, Pinheiro CCG, Almeida MCA, Oliveira CRGCM, Coudry RA, Rocha DL, Bueno DF. Deciduous dental pulp stem cells for maxillary alveolar reconstruction in cleft lip and palate patients. *Stem Cells Int*. 2020;2020:6234167. doi: 10.1155/2020/6234167.
46. Alkaabi SAOA. Regenerative medicine for alveolar cleft treatment. 2023.
47. Kanwal L, Khawaja M, Idrees W, Sukhia RH, Fida M. The implication of stem cell therapy in cleft lip and palate and other craniofacial anomalies – a literature review. *J Calif Dent Assoc*. 2023;51(1):2246192.
48. Amiri MA, Lavaee F, Danesteh H. Use of stem cells in bone regeneration in cleft palate patients: review and recommendations. *J Korean Assoc Oral Maxillofac Surg*. 2022;48(2):71-78. doi: 10.5125/jkaoms.2022.48.2.71.

Endereço para correspondência:

Mateus Cardoso Oliveira
 Av. José Moreira Sobrinho, s/n Jequiezinho
 CEP 45205-490 – Jequié, Bahia, Brasil
 Telefone: +5577998484898
 E-mail: mateus_oc1@hotmail.com

Recebido em: 05/10/2024. Aceito: 24/10/2025.