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Clinical considerations of regenerative processes in bucomaxillofacial surgery using stem cells from exfoliated deciduous teeth: a systematic review

Maria Eduarda Chaves Gomes[1,*], **Heitor Nogueira**[1], **Igor Mariotto Beneti**[1]

[1] UNORTE - University Center of Northern São Paulo - Dentistry department- Bucomaxillofacial surgery, Sao Jose do Rio Preto, Sao Paulo, Brazil.

*Corresponding author: Maria Eduarda Gomes.
UNORTE - University Center of Northern São Paulo -
Dentistry department- Bucomaxillofacial surgery,
Sao Jose do Rio Preto, Sao Paulo, Brazil.
E-mail: m.eduardagomes@outlook.com.br
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Abstract

Introduction: The World Health Organization forecasts that road accidents will be the third cause of facial trauma worldwide by 2025. To catalyze regenerative processes in oral and maxillofacial surgery, human oral mesenchymal stem cells (Stem Cells from Exfoliated Deciduous Teeth - SHEDs) have been discovered near the oral mucosal tissues and primary teeth. **Objective:** It was to analyze the main clinical considerations of regenerative processes in bucomaxillofacial surgery using stem cells from exfoliated deciduous teeth. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from July to August 2025 in the Web of Science, Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=78.7%>50%. A total of 122 articles were found and submitted to eligibility analysis, with 14 final studies selected to compose the results of this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR2. The conclusion was that the integration of SHED cells with scaffolds consistently improves alveolar and maxillary bone regeneration compared to scaffold-only approaches, resulting in increased bone volume, density, osteogenesis, and angiogenesis. Thus, SHEDs have emerged as a promising alternative in regenerative and reconstructive medicine. These stem cells exhibit high differentiation potential and self-renewal capacity. These stem cells can be easily harvested from accessible and numerous sources, such as molars and extracted baby teeth, with minimal invasiveness, playing essential roles in clinical applications and pointing to the overcoming of complex challenges in restorative and reconstructive medicine.

Keywords: Stem Cells. Exfoliated Deciduous Teeth. SHED. Bucomaxillofacial. Surgery. Regeneration.

Introduction

The World Health Organization forecasts that in 2025 road accidents are the third cause of facial trauma in the world [1]. The lack of bone in the alveolar borders has been a great problem in the functional aesthetic recovery in patients who have undergone dentoalveolar traumatisms, traumatic dental extractions, congenital dental absence, pathologies involving maxilla and mandible [2].

In this context, to catalyze regenerative processes in oral and maxillofacial surgery, Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs) have been discovered near oral mucosal tissues and primary (SHEDs) and secondary (permanent) teeth. All of these different stem cell types have the ability to divide and self-renew. Due to their relative accessibility, these cell types may constitute a stem cell source with substantial potential for application in tissue regeneration [3].

Furthermore, defects and abnormalities in skull, jaw, and facial tissues due to various physiological problems, such as speech, chewing, and swallowing disorders, cause disease and psychological effects, posing significant public health challenges. Therefore, SHEDs have emerged as a promising alternative in regenerative and reconstructive medicine. These stem cells exhibit high differentiation potential and selfrenewal capacity. These stem cells can be easily harvested from numerous accessible sources, such as molars and extracted primary teeth, with minimal invasiveness. They play essential roles in clinical applications and point to overcoming complex challenges in restorative and reconstructive medicine [4].

SHEDs have been shown to have a higher proliferation rate and increased cell population doubling when compared to stem cells from permanent teeth. Therefore, using them in tissue engineering may be advantageous over stem cells from adult human teeth. To characterize SHEDs by immunophenotyping, the surface antigens CD-73, CD-90, and CD-105, which are known to be present in mesenchymal lineages, were positively expressed in SHEDs according to flow cytometry analysis, while CD-34, CD-45, and HLA-DR were not [5].

Also, among the various sources of stem cells, the tooth pulp provides mesenchymal stem cells, multipotent and immunocompatible, that is, they can serve not only the donor but also the whole family [6]. Stem cells are cells that differentiate, giving rise to new cells of good quality, which can originate osteoblasts and, thus, achieve bone integration in less time for a dental implant, and maxillary bone elevation, and be able to reconstruct the dentin, in relation to tissue lesions [6,7].

In this context, stem cells of dental origin have tissue regeneration capacity and still induce bone regeneration of the maxilla. Therefore, they are indicated for treatments of degenerative diseases like traumatic bone loss [8]. The collection of the milk tooth is done during the period of changing the child's teeth between 5 to 12 years. With this, we conclude that the tooth is not an invasive process because the collection is only done when the tooth begins to exfoliate [9,10].

Therefore, this systematic review analyzed the main clinical considerations of regenerative processes in bucomaxillofacial surgery, using stem cells from exfoliated deciduous teeth.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed at: 08/15/2025. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed at: 08/15/2025.

Search Strategy and Search Sources

The literature search process was carried out from July to August 2025 and developed based on Web of Science, Embase, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH terms): *"Stem Cells. Exfoliated Deciduous Teeth. SHED. Bucomaxillofacial. Surgery. Regeneration",* and the Boolean "and" was used between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Summary of Findings

A total of 122 articles were found and submitted to eligibility analysis, with 14 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=78.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2.

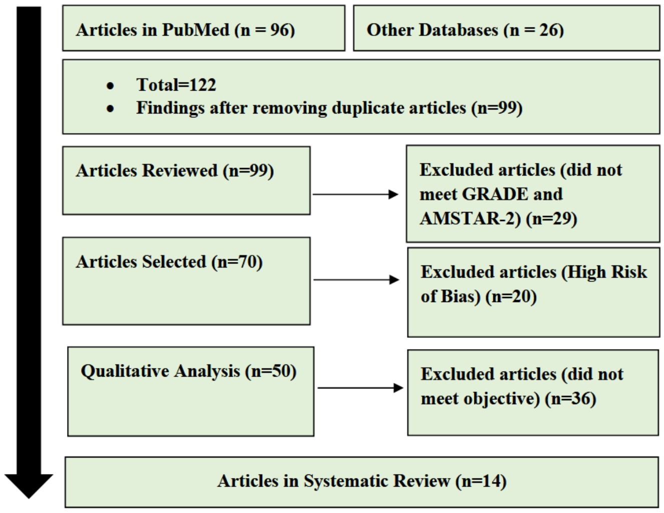

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

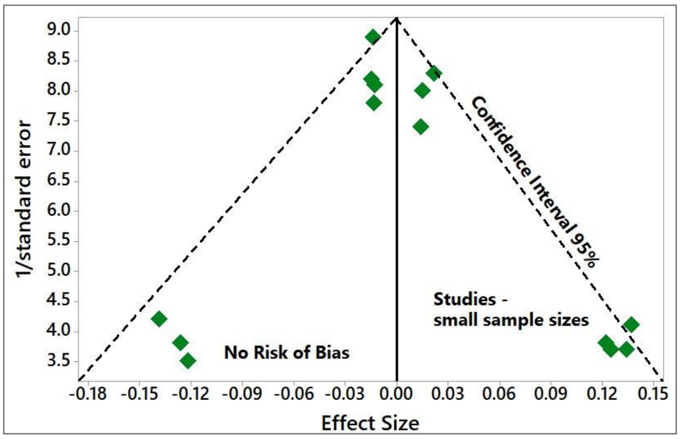

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=14 studies). Source: Own Authorship.

Major Results

The SHEDs (stem cells from human exfoliated deciduous teeth) were first obtained by Miura et al. (2003) [11] and are able to differentiate into adipocytes, chondroblasts, osteoblasts, odontoblasts, and muscle cells in vitro. In addition, they can also differentiate into neural cell lines. *In vivo*, SHED does not differentiate directly into osteogenic cells, but they induce bone formation and assist in the process of angiogenesis [11-13]. Furthermore, SHED has a higher rate of cell proliferation, shorter population doubling time and a clonogenic potential. As for the expression of surface markers, these two cell types are similar, being mesenchymal and negative markers for hematopoietic markers [13].

For the collection to be possible, it is necessary to register the dental surgeon to a cryogenic center and the authorization of those responsible for the donor child. The procedure should be performed in patients aged 6 to 12 years during the dental exfoliation phase, and the elements should not present carious lesions [14]. Preceded by intra and extraoral antisepsis, the element (s) are extracted, with the shortest time and contact with the saliva, respecting strictly the aseptic chain. After removal of any adherent soft tissues, the elements are immersed in DMEM culture medium maintained at 4 to 8 °C and directed to a laboratory for isolation and culture of the stem cell [15].

After isolated and cultured, because they are mesenchymal stem cell, can be used for the therapy of the most diverse pathologies of the nervous system, vascular system, heart, skin, pancreas, liver, eyes, muscles, lungs, kidneys, cartilage, intestines, bones, among others. The SHEDs acquired by this process can be stored indefinitely, being 100% compatible with the donor and relatives, making it impossible to reject them, besides allowing 20 possibilities of collection per child [16].

There is evidence that stem cells from deciduous teeth are similar to those found in the umbilical cord [17]. When compared to stem cells from the bone marrow and pulp of permanent teeth, SHEDs showed a higher rate of proliferation. In addition, data from this study indicate that SHEDs have the ability to differentiate into functional odontoblastic cells, adipocytes and neural cells, and stimulate osteogenesis after *in vivo* transplantation. Research has shown that pulp stem cells require an appropriate inducing medium and a framework composed of hydroxyapatite/ tricalcium phosphate to induce the formation of bone, cement, and dentin *in vivo* [18].

Effective alveolar and maxillary bone regeneration can be promoted by SHEDs. Alshaibani et al. (2025) [19] conducted a systematic review and analyzed eight studies focusing on bone regeneration using SHEDs. The results revealed that scaffolds seeded with SHEDs showed regeneration rates of 32.64% and 40%, significantly higher than the control. The integration of SHEDs cells with scaffolds consistently improves alveolar and maxillary bone regeneration compared to scaffold-only approaches, increasing bone volume, density, osteogenesis, and angiogenesis.

Ribeiro et al. (2024) [20] established a proof-of-concept model system for the biological healing of periapical lesions using SHEDs spheroids that were cultured as a 2D monolayer and then as 3D multicellular spheroids. The results showed that, compared with cells grown in monolayers, the spheroids exhibited uniform cellularity and greater viability within the lesion cavity, which was accompanied by a temporal reduction in the expression of CD13, CD29, CD44, CD73, and CD90 mRNAs, typically expressed by stem cells. Concomitantly, the expression of markers that characterize osteoblastic differentiation (RUNX2, ALP, and BGLAP) increased.

Some authors have demonstrated the formation of autologous fibrous bone tissue from stem cells from pulps of individuals over the age of 30 years, as well as the differentiation of these cells into odontoblasts. The markers for the stem cells are of extreme importance because these cells reside in different places inside the tissue. Further studies are needed on specific markers that can identify niches of stem cells present in the dental pulp in situ and on how the development of these niches occurs. It is possible that stem cells from the human pulp and periodontal ligament are associated with the microvasculature [21].

The following microvascular markers are currently used for the localization of such cells STRO-1 (stromal cell marker), Von Willebrand Factor and CD146 (endothelial cell surface molecule). The expression of cellular telomerase in normal tissues seems to be associated with the presence of stem cells. In situ detection techniques of this ribonucleoprotein have the possibility to act as cellular markers [21].

In addition, researchers cultivated bone marrow and human pulp stem cells from impacted third molars and analyzed the gene expression of these cells through the Microarray cDNA method. A highly similar gene pattern has been demonstrated between these two cell types, with the exception of a few genes, including IGF-2 (insulin-like growth factor-2) and type XVIII collagen 1, however, the expression of this difference is unknown [22].

Dental morphogenesis involves a series of dynamic and reciprocal interactions between the ectoderm and the mesenchyme. Growth factors are extracellularly secreted proteins that govern morphogenesis during such interactions and comprise five protein families bone morphogenetic protein (BMPs); growth factors for fibroblasts (FGFs); Hedgehog proteins (Hhs), wingless and int-related proteins (Wnts), and tumor necrosis factor (TNF) [22].

Although these distinct families are involved in dental development, BMPs are sufficient for the formation of tertiary dentin. Some authors have further demonstrated that calcium-hydroxide-induced pulp regeneration is mediated by Notch cell-cell signaling. The results were consistent to affirm that this signaling controls the fate of stem cells from the pulp during its regeneration [23].

Finally, BMPs are also expressed in the starry enamel organ epithelium during the hood phase and are associated with the differentiation of ameloblasts and odontoblasts. Growth hormone may induce the expression of these BMPs during tooth formation. At the onset of dental morphogenesis, BMP-2, BMP4 and BMP-7 act as important epithelial flags that regulate differentiation of neural crest-derived mesenchyme in an odontogenic lineage. Such flags still determine the number and position of the tooth cusps [24].

Limitations

Robust randomized controlled clinical studies with significant observational follow-up are lacking.

Conclusion

The conclusion was that the integration of SHED cells with scaffolds consistently improves alveolar and maxillary bone regeneration compared to scaffold-only approaches, resulting in increased bone volume, density, osteogenesis, and angiogenesis. Thus, SHEDs have emerged as a promising alternative in regenerative and reconstructive medicine. These stem cells exhibit high differentiation potential and self-renewal capacity. These stem cells can be easily harvested from accessible and numerous sources, such as molars and extracted baby teeth, with minimal invasiveness, playing essential roles in clinical applications and pointing to the overcoming of complex challenges in restorative and reconstructive medicine.

CRediT

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Informed Consent

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

Application of Artificial Intelligence (AI)

Not applicable.

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References

1. Miteva M, Mihaylova Z, Mitev V, Aleksiev E, Stanimirov P, Praskova M, Dimitrova VS, Vasileva A, Calenic B, Constantinescu I, Perlea P, Ishkitiev N. A Review of Stem Cell Attributes Derived from the Oral Cavity. Int Dent J. 2024 Oct;74(5):1129-1141. doi: 10.1016/j.identj.2024.03.008.
2. Zhu SY, Yuan CY, Lin YF, Liu H, Yang YQ, Wong HM, Zhang CF, Wang PL, Gu M. Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs) and Dental Pulp Stem Cells (DPSCs) Display a Similar Profile with Pericytes. Stem Cells Int. 2021 Jul 24;2021:8859902. doi: 10.1155/2021/8859902.
3. Ahmed A, Qabool H, Habib S, Fida M, Rukh Shah SG. Mesenchymal stem cells and its translation into clinical orthodontics: current trends and future perspectives. J Pak Med Assoc. 2023 Feb;73(Suppl 1)(2):S62-S68. doi: 10.47391/JPMA.AKUS-10.
4. Entezami S, Sam MR. The role of mesenchymal stem cells-derived from oral and teeth in regenerative and reconstructive medicine. Tissue Cell. 2025 Apr;93:102766. doi: 10.1016/j.tice.2025.102766.
5. Yumkham R, Nagarathna C, Sanjenbam N, Gopilal Singh A, Philip Singh H, Ashem A. Isolation and characterization of stem cells from human exfoliated deciduous teeth. Bioinformation. 2024 May 31;20(5):557-561. doi: 10.6026/973206300200557.
6. Ding J, Sun Z, Ma L, Wang L, Liao Z, Liang L, Yang H, Mao R. Microspheres of stem cells from human exfoliated deciduous teeth exhibit superior pulp regeneration capacity. Dent Mater. 2025 Jan;41(1):70-80. doi: 10.1016/j.dental.2024.10.015.
7. Shang L, Shao J, Ge S. Immunomodulatory functions of oral mesenchymal stem cells: Novel force for tissue regeneration and disease therapy. J Leukoc Biol. 2021 Sep;110(3):539-552. doi: 10.1002/JLB.3MR0321-766R.
8. Dong N, Zhang C, Zhang Q, Bao S, Hu Y, Xu H, Dai P, Li C, Li S, Wu P, Xu J, Cai X, Wang Z, Luo L. A cell-free SHED lysate-hydrogel system for oral ulcer healing with anti-inflammatory and pro-angiogenic effects. J Nanobiotechnology. 2025 Jul 28;23(1):547. doi: 10.1186/s12951-025-03597-3.
9. Anoop M, Datta I. Stem Cells Derived from Human Exfoliated Deciduous Teeth (SHED) in Neuronal Disorders: A Review. Curr Stem Cell Res Ther. 2021;16(5):535-550. doi: 10.2174/1574888X16666201221151512.
10. Su J, Ge X, Jiang N, Zhang Z, Wu X. Efficacy of Mesenchymal Stem Cells from Human Exfoliated Deciduous Teeth and their Derivatives in Inflammatory Diseases Therapy. Curr Stem Cell Res Ther. 2022;17(4):302-316. doi: 10.2174/1574888X17666220417153309.
11. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, Shi S. SHED: stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci USA, Washington, D.C., v. 100, no. 10, p. 5807-5812, 2003.
12. Haque N, Kasim NHA. Stem Cells from Human Exfoliated Deciduous Teeth: Waste to Wealth. Curr Stem Cell Res Ther. 2021;16(5):493-494. doi: 10.2174/1574888X1605210616151801.
13. Mahdavi-Jouibari F, Parseh B, Kazeminejad E, Khosravi A. Hopes and opportunities of stem cells from human exfoliated deciduous teeth (SHED) in cartilage tissue regeneration. Front Bioeng Biotechnol. 2023 Feb 13;11:1021024. doi: 10.3389/fbioe.2023.1021024.
14. Behr B, Ko SH, Wong VW, Gurtner GC, Longaker

MT. Stem cells. Plast Reconstr Surg. 2010;126(4):1163-71.
15. Ashri NY, Ajlan SA, Aldahmash AM. Dental pulp stem cells. Biology and use for periodontal tissue engineering. Saudi Med J. 2015;36(12):1391- 9.
16. De Sá Silva F, Almeida PN, Rettore JVP, Maranduba CP, de Souza CM, de Souza GT, et al. Toward personalized cell therapies by using stem cells: seven relevant topics for safety and success in stem cell therapy. J Biomed Biotechnol. 2012;2012:758102.
17. Glenn JD, Whartenby KA. Mesenchymal stem cells: Emerging mechanisms of immunomodulation and therapy. World J Stem Cells. 2014; 6(5):526-39. 10. Potdar PD, Jethmalani YD. Human dental pulp stem cells: Applications in future regenerative medicine. World J Stem Cells. 2015;7(5):839-51.
18. Yang J, Yuan G, Chen Z. Pulp Regeneration: Current Approaches and Future Challenges. Front Physiol. 2016;7:58.
19. Alshaibani DA, Kamadjaja MJ, Sitalaksmi RM, Ridwan RD, Al-Gabri RS, Zafar MS, Ramalingam S, Alqutaibi AY. Regenerative potential of human dental pulp stem cells in scaffold-based alveolar and jaw bone reconstruction: a systematic review. BMC Oral Health. 2025 Jul 2;25(1):986. doi: 10.1186/s12903-02506368-6.
20. Ribeiro VL, Dernowsek JA, Fernandes RR, Pitol DL, Issa JPM, Mazzi-Chaves JF, Bombonato-Prado KF, Sousa-Neto MD, Passos GA. Repopulation of a 3D simulated periapical lesion cavity with dental pulp stem cell spheroids with triggered osteoblastic differentiation. Braz Dent J. 2024 Dec 16;35:e235847. doi: 10.1590/0103-644020235847.
21. Feques R dos R, Freitas SAA, Pereira ALA, Vasconcelos A de F. Uso de célulastronco na Odontologia: realidade ou utopia? Braz J Periodonto 2014;24(03):2430.
22. Gong T, Heng BC, Lo ECM, Zhang C. Current Advance and Future Prospects of Tissue Engineering Approach to Dentin/Pulp Regenerative Therapy. Stem Cells Int. 2016;2016:9204574.
23. Chen F-M, Gao L-N, Tian B-M, Zhang X-Y, Zhang Y-J, Dong G-Y, et al. Treatment of periodontal intrabony defects using autologous periodontal ligament stem cells: a randomized clinical trial. Stem Cell Res Ther. 2016;7:33.
24. Yang J, Yuan G, Chen Z. Pulp Regeneration: Current Approaches and Future Challenges. Front Physiol. 2016;7:58.

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