Indonesian Journal of Dental Medicine
Volume 6 Issue 1 2023; 43-46

Literature Review

Current approaches of salivary glands regeneration for management of xerostomia and hyposalivation: A narrative review

Fatma Yasmin Mahdani, Nurina Febriyanti Ayuningtyas
Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Background: The salivary glands are the organs that produce saliva and have a role keeping the oral cavity moist and lubricated. Salivary glands regeneration is important for developing treatments on management of xerostomia and hyposalivation because of the irreversible damage of salivary glands. Common causes include aging, polypharmacy, autoimmune disease, including Sjogren's syndrome, and head and neck radiation, in which xerostomia and hyposalivation having a substantial impact on patient health and wellbeing. **Purpose:** To describe current approach of salivary glands regeneration for management of xerostomia and hyposalivation through narrative review. **Review:** A literature search using Science Direct and PubMed yielded results between 1973 and 2022, and the results were evaluated to identify the most promising approaches and for future research. The keywords of the search strategy were "salivary gland regeneration" and "xerostomia" or "hyposalivation". Current studies have revealed potential targets in the development of salivary gland regeneration for the management of xerostomia and hyposalivation. Stem cells therapy aims to repair damaged at the cellular level, especially stimulating acini cells, multiplying and differentiating to replace dead or damaged acini cells. Bioengineering is through isolated acini cells cultured on many modified cell line and administration of bioactive compounds. Gene therapy aims to rebuild functional water channels and neutralization of inflammatory mediators. **Conclusion:** Several approaches of salivary glands regeneration that can be taken are stem cells therapy, bioengineering, and gene transfer.

Keywords: salivary glands regeneration; xerostomia; hyposalivation; medicine; dentistry

Correspondence: Fatma Yasmin Mahdani, Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga. Jl. Mayjen Prof. Dr. Moestopo 47 Surabaya, 60132 Indonesia. Email: fatmayasminmahdani@fkg.unair.ac.id

INTRODUCTION

The salivary glands have important structures and functions in the oral cavity. Various diseases, such as infectious diseases, autoimmune disorders, physical trauma to tumors and cancer, can change the function of the salivary glands and impact the patient's quality of life (QoL). Xerostomia or dry mouth, is a subjective complaint which is often accompanied by a decrease in the amount of salivary secretion or hyposalivation. Hyposalivation can be measured objectively through a sialometry.[1,2] Xerostomia is one of the symptoms that arise due to salivary gland hypofunction, it can be caused by aging, side effects of using drugs, autoimmune disorders or effects of gland and neck radiation. Salivary glands regeneration is important for developing treatments on manage xerostomia and hyposalivation because of the irreversible damage of salivary glands.[1,3–6] A literature search using Science Direct and PubMed yielded results between 1973 and 2022, and the results were evaluated to identify the most promising approaches and for future research. The keywords of the search strategy were "salivary gland regeneration" and "xerostomia" or "hyposalivation". Furthermore, the objective of this review is to describe the current approach of salivary glands regeneration for management of xerostomia and hyposalivation.

REVIEW

Salivary Glands

The salivary glands consist of 3 main pairs of salivary glands, namely the parotid, submandibular and sublingual glands. And minor salivary glands numbering about 600 to 1000 are located in the labial mucosa and buccal mucosa, palate, lingual, floor of the mouth and retromolar of the oral mucosa.[1,2,7,8] The salivary glands are composed of parenchyma and stroma constituents. The parenchyma consists of secretory endings, called acini cells, which secrete primary saliva. Acini cell connected to intercalated

DOI: https://doi.org/10.20473/ijdm.v6i1.2023.43-46

duct, striated duct, and secretory duct that a system of ducts that modify salivary product. Acini cells are composed of serous or mucous cells, or mucus cells but lined by serous cells.[9–12]

Histologically, the salivary glands are classified according to their structure, composition and secretion. All ductal systems have ductal lengths and diameters that vary depending on the type of gland. There are three kinds of ductal segments, namely intercalated ducts, striated ducts and excretory ducts, which belong to the major salivary glands. All three have long and branching ducts, but the difference is that the sublingual and minor glands do not have striated ducts while the other glands have all duct segments.[2,12–14]

Myoepithelial cells are one of the systems that support the process of salivary secretion, contractile cells that have a star-shaped structure that surrounds the acini and intercalated ducts in the salivary glands. Myoepithelial cells are innervated by the autonomic nervous system and have a role in communicating with salivary flow by compressing the acini and ducts during contraction, and also providing structural resistance to the parenchyma during secretion.[7,8,15–17]

Almost all the protein in the salivary glands, comes purely from the acini cells of the salivary glands and not from the bloodstream. In contrast to whole saliva, there are about 2.500 proteins in whole saliva mixed with desquamated epithelial cells, gingival crevicular fluid and intraoral microorganisms and only 10% is estimated to be derived from the salivary glands. Whole saliva in the oral cavity has a composition of more than 99% water and less than 1% protein and salt. Every day, the normal production of saliva every day is about 0.6 L and produced by the major salivary glands is about 90% and the minor glands are less than 10% of secretions.[1,18,19]

Xerostomia

Xerostomia or dry mouth is caused by salivary gland dysfunction, which can be in the form of disturbances in the quantity or quality of saliva produced and can result in hyposalivation, as well as changes in saliva composition. It is estimated that 5% to 46% of the general population suffer from xerostomia, with precipitating factors including age, gender, stress, degenerative diseases and medications contributing to decreased salivary secretion. Aging is a physiological cause of xerostomia. In addition, drugs can also cause considerable xerostomia, Sjögren's syndrome and head-and-neck radiation therapy also cause the majority of xerostomia cases.[1,5,9,20]

Current treatments for xerostomia can be divided into four main categories: (1) preventive therapy; (2) symptomatic treatment (palliative); (3) local or topical salivary stimulation; and (4) systemic salivary stimulation. Successful therapy of xerostomia and hyposalivation often involves a combination of agents based to the patient's needs. Transcutaneous electrical nerve stimulation and acupuncture as alternative approaches are also being studied, but must be supported by increased water consumption or fluid requirements and we are exclude in this review. This review provides the current approaches of salivary glands regeneration, as such stem cells therapy, bioengineering, and gene transfer and provide illustration of brief mechanism each salivary glands regeneration.[1,21,22]

Permanent damage causing irreversible damage the salivary glands can result in impaired production and function of the salivary glands. Permanent damage to the salivary acini secreting cells of the salivary glands or loss of innervating signals causes xerostomia, and hyposalivation. Currently, there is no remedy and xerostomia has a severe impact on the health and well-being of patients. Oral function can also be impaired, speaking, eating, swallowing, chewing food and tasting food, has a major impact on the patient's health, QoL, and health care costs. And the importance of salivary gland regenerative therapy is expected to improve the patient's QoL.

Stem Cells Therapy

The use of stem cell therapy, is a promising and promising regenerative therapeutic approach, not only for the salivary glands but also for other organs as a whole. Stem cell therapy based approaches have been used worldwide and are currently being implemented and have an 11.9% success rate of clinical intervention for xerostomia. Stem cells derived from mesenchymal tissue are the most frequently used source of stem cells, also because of their most abundant availability and ability to harvest them in non-invasive treatments. Mesenchymal stem cells are stem cells taken from bone marrow, adipose tissue, or umbilical cord blood, or it can be from tissue in teeth. There have been no reports on the long-term safety of interventional mesenchymal stem cell transplantation, but it has the potential to metastasize to other tissues or organs. In addition, its use has the potential to cause excessive tissue fibrosis, and its verious properties and effectiveness based on the source of the stem cells.[3,4,11,23–25]

Stem cells therapy aims to repair damaged at the cellular level, they stimulating acini cells, multiplying and differentiating to replace dead or damaged acini cells. The approach principle for stem cell transplantation interventions is to encourage endogenous stem cell or progenitor cells (eg, SOX2+, KRT14+ and 15+) or late-differentiating cells (eg, MIST1+) to recruit tissue. In addition, the support of the nervous system, blood vessels and nutrition, maintain signalling pathway, as well as promoting ductal cells is very necessary in the regeneration of the salivary glands.[3,4,11,23–25]

Bioengineering acini cells

Another regenerative strategy is through the use of biotechnology to regenerate salivary glands. Acini cells isolated from salivary glands cultured on many modified cell lines were able to implant into murine submandibular glands, particularly around the ducts, after ductal ligation injury. The success effectiveness of cells transplanted by salivary engraftment into recipients is still far from optimal, therefore, a number of studies have been carried out to

DOI: https://doi.org/10.20473/ijdm.v6i1.2023.43-46

optimize signalling methods and the cellular environment to enhance engraftment.[12,19]

Transplantation of bioactive compounds directly into salivary glands is a potential therapeutic option, including administration and injection into the main duct, which has previously been done for the delivery of many active ingredients, including growth factors, primary cells, cytokines, or antioxidants via adenoviral vectors.[12,19,26]

Gene therapy

Gene therapy that has been carried out has a principle approach to rebuilding functional water channel and neutralizing inflammatory mediators. Some diseases with salivary gland dysfunction usually have a reduction in the number of functional water channel, therefore this therapy has the potential and aims to rebuild the water channel to increase fluid permeability and increase salivary secretion. For example, human AQP1 gene transplantation interventions via adenovirus are being developed.[12,27–31]

Neutralization of inflammatory mediators is also an approach that can be done through gene therapy. This is a potential treatment option for patients with inflammatory salivary gland diseases, such as Sjögren's syndrome. Neutralization of B cell activating factor and proliferation-inducing ligands led to a significant reduction in CD138+ inflammatory cells. Decreases in the amount of IgG and IgM in the saliva produced by the salivary glands have also been reported. This therapy also has its own challenges despite reported increasing efficacy, including the risk of recipients increasing immune responses, and the development of inflammation, off-target effects, and insertion mutagenesis, which require further research.[12,27–29]

CONCLUSION

The success of xerostomia therapy is still a topic of research and in the clinical world, so it is still being developed. Several approaches of salivary glands regeneration that can be taken are stem cells therapy, bioengineering, and gene transfer.

ACKNOWLEDGEMENT

The authors thank to Oral Medicine Study Program and Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga.

REFERENCES

1. Glick M, Greenberg MS, Lockhart PB, Challacombe SJ. Burket's Oral Medicine. 13th Edition. Hoboken, editor. USA: John Wiley & Sons; 2021. 1136 p.
2. Edgar M, Dawes C, O'Mullane D. Saliva and Oral Health. 4th ed. Duns Tew: Stephen Hancocks Limited; 2015.
3. Yoo C, Vines JB, Alexander G, Murdock K, Hwang P, Jun H-W. Adult stem cells and tissue engineering strategies for salivary gland regeneration: a review. Biomater Res. 2014;18:9.
4. D'Agostino C, Elkashty OA, Chivasso C, Perret J, Tran SD, Delporte C. Insight into Salivary Gland Aquaporins. Cells. 2020 Jun 25;9(6):1547.
5. Quock RL. Xerostomia: current streams of investigation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Jul;122(1):53–60.
6. Delli K, Spijkervet FKL, Vissink A. Salivary gland diseases: infections, sialolithiasis and mucoceles. Monogr Oral Sci. 2014;24:135–48.
7. Roblegg E, Coughran A, Sirjani D. Saliva: An all-rounder of our body. Eur J Pharm Biopharm. 2019 Sep;142:133–41.
8. Carpenter GH. The secretion, components, and properties of saliva. Annu Rev Food Sci Technol. 2013;4:267–76.
9. Jensen SB, Vissink A, Limesand KH, Reyland ME. Salivary Gland Hypofunction and Xerostomia in Head and Neck Radiation Patients. J Natl Cancer Inst Monogr. 2019;2019(53).
10. Pedersen A, Sørensen CE, Proctor GB, Carpenter GH. Salivary functions in mastication, taste and textural perception, swallowing and initial digestion. Oral Dis. 2018 Nov;24(8):1399–416.
11. Piraino LR, Benoit DSW, DeLouise LA. Salivary Gland Tissue Engineering Approaches: State of the Art and Future Directions. Cells. 2021;10(7):1723.
12. Rocchi C, Emmerson E. Mouth-Watering Results: Clinical Need, Current Approaches, and Future Directions for Salivary Gland Regeneration. Trends Mol Med. 2020;26(7):649–69.
13. Aframian DJ, Keshet N, Nadler C, Zadik Y, Vered M. Minor salivary glands: Clinical, histological and immunohistochemical features of common and less common pathologies. Acta Histochem. 2019 Nov;121(8):151451.
14. Akintoye SO, Mupparapu M. Clinical Evaluation and Anatomic Variation of the Oral Cavity. Dermatol Clin. 2020 Oct;38(4):399–411.
15. Nanci A. Ten Cate's Oral Histology. 9th ed. St. Louis: Elsevier; 2018.
16. Bellagambi FG, Lomonaco T, Salvo P, Vivaldi F, Hangouët M, Ghimenti S, et al. Saliva sampling: Methods and devices. An overview. TrAC Trends Anal Chem. 2020 Mar;124:115781.
17. Uchida H, Ovitt CE. Novel impacts of saliva with regard to oral health. J Prosthet Dent. 2022 Mar;127(3):383–91.
18. Pedersen AML, Sørensen CE, Proctor GB, Carpenter GH, Ekström J. Salivary secretion in health and disease. J Oral Rehabil. 2018 Sep;45(9):730–46.
19. Porcheri C, Mitsiadis TA. Physiology, Pathology and Regeneration of Salivary Glands. Cells. 2019;8(9).
20. Nugraha AP, Ernawati DS, Harijanti K, Parmadiati AE. Psychological Stress Induced Xerostomia and Hyposalivation: The Case Study in Indonesian Female Patient. J Int Dent Med Res. 2018;12(1):216–9.
21. Mulyani SWM, Astuti ER, Wahyuni OR, Ernawati DS, Ramadhani NF. Xerostomia Therapy Due to Ionized Radiation Using Preconditioned Bone Marrow-Derived Mesenchymal Stem Cells. Eur J Dent. 2019 May;13(2):238–42.
22. Łysik D, Niemirowicz-Laskowska K, Bucki R, Tokajuk G, Mystkowska J. Artificial Saliva: Challenges and Future Perspectives for the Treatment of Xerostomia. Int J Mol Sci. 2019 Jun 29;20(13):3199.
23. Narmada IB, Laksono V, Nugraha AP, Ernawati DS, Winias S, Prahasanti C, et al. Regeneration of Salivary Gland Defects of Diabetic Wistar Rats Post Human Dental Pulp Stem Cells Intraglandular Transplantation on Acinar Cell Vacuolization and Interleukin-10 Serum Level. Pesqui Bras

Odontopediatria Clin Integr. 2019;19(1):1–10.
24. Suciadi SP, Nugraha AP, Ernawati DS, Ayuningtyas NF, Narmada IB, Prahasanti C, et al. The Efficacy of Human Dental Pulp Stem Cells in regenerating Submandibular Gland Defects in Diabetic Wistar Rats (Rattus novergicus). Res J Pharm Technol. 2019;12(4):1573.
25. Xia J, Minamino S, Kuwabara K, Arai S. Stem cell secretome as a new booster for regenerative medicine. Biosci Trends. 2019;13(4):299–307.
26. Chansaenroj A, Yodmuang S, Ferreira JN. Trends in Salivary Gland Tissue Engineering: From Stem Cells to Secretome and Organoid Bioprinting. Tissue Eng Part B Rev. 2021;27(2):155–65.
27. Sisto M, Ribatti D, Lisi S. Aquaporin water channels: New perspectives on the potential role in inflammation. Adv Protein Chem Struct Biol. 2019;116:311–45.
28. Azad AK, Raihan T, Ahmed J, Hakim A, Emon TH, Chowdhury PA. Human Aquaporins: Functional Diversity and Potential Roles in Infectious and Non-infectious Diseases. Front Genet. 2021;12:654865.
29. Salman MM, Kitchen P, Yool AJ, Bill RM. Recent breakthroughs and future directions in drugging aquaporins. Trends Pharmacol Sci. 2022;43(1):30–42.
30. Liao S, Gan L, Lv L, Mei Z. The regulatory roles of aquaporins in the digestive system. Genes Dis. 2021 May;8(3):250–8.
31. Meli R, Pirozzi C, Pelagalli A. New Perspectives on the Potential Role of Aquaporins (AQPs) in the Physiology of Inflammation. Front Physiol. 2018;9:101.

DOI: https://doi.org/10.20473/ijdm.v6i1.2023.43-46