Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Indian Citation Index (ICI) Index Copernicus value = 100

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

Unraveling the Mysteries of Oral Submucous Fibrosis: A Systematic Review

[1]Hitesh Vadera, [2]Deval Mehta, [3]Ramita Sood, [4]Divya Jain

[1]PhD Scholar, Gujarat University, Ahmedabad, Gujarat, India;
[2]Dean and Head of Department, Oral and Maxillofacial Surgery, Bopal Dental College, Ahmedabad, Gujarat, India;
[3]Head of Department, Oral and Maxillofacial Surgery, AMC Dental College, Khokhra, Ahmedabad, Gujarat, India;
[4]AMC Dental College, Khokhra, Ahmedabad, Gujarat, India

ABSTRACT:
Oral submucous fibrosis (OSF) is a collagen deposition disorder that affects a patient's oral function and quality of life. It may also potentially transform into malignancy. This review summarizes the risk factors, pathogenic mechanisms, and treatments of OSF based on clinical and bio-molecular evidence.

Received: 10 April, 2023 Accepted: 13 May, 2023

Corresponding author: Hitesh Vadera, PhD Scholar, Gujarat University, Ahmedabad, Gujarat, India

This article may be cited as: Vadera H, Mehta D, Sood R, Jain D. Unraveling the Mysteries of Oral Submucous Fibrosis: A Systematic Review. J Adv Med Dent Scie Res 2023;11(6):68-70.

INTRODUCTION

Oral submucous fibrosis (OSF) is a common oral precancerous lesion in Asian countries, especially in areas with a culture of chewing betel nuts. OSF is caused by abnormal collagen deposition in the connective tissues and affect mouth functions. Although there is no immediate danger with a diagnosis of OSF, it seriously affects the quality of life of patients. OSF interferes with a patient's quality of life because of annoying symptoms, such as ulceration, xerostomia, a burning sensation, and limitation in mouth opening.[1] Moreover, OSF is a pre-malignant disorder with the potential for malignant transformation. Therefore, it is necessary to understand its clinical features, prevalence, malignant transformation rate, and risk factors. In Asia, the major risk factor for OSF is betel nut chewing. To reduce the occurrence of OSF, it is important to discover the pre-malignant disorder in the early stage, and understand the pathologic mechanism and treatment options.[2]This review introduces OSF from both clinical and molecular perspectives and focuses on the epidemiology, diagnostic biomarkers, mechanisms of OSF induction and transformation, and aggressive therapeutic interventions.

CLINICAL FEATURES

The oral mucosa can be divided into masticatory, specialized, and lining mucosa based on their function and histology. OSF occurs on all three types of mucosae, and most frequently occurs in the buccal mucosaretromolar area, and the soft palate sites. The symptoms of OSF include dry mouth, pain, taste disorders, restricted tongue mobility, trismus, dysphagia, and changed tone movability. In addition to the oral cavity, the fibrosis even involves the pharynx and esophagus. In OSF cases, the soft and pink oral mucosa initially becomes inelastic and slightly blanched. Subsequently, the mucosa becomes markedly inelastic and opaque, with white blanching, and appears papery white and tough on palpation, with a firm vertical band, which can be felt just opposite the premolar region. In the later stages, the lips and palate are also involved with lesions occurring on one or more sites. Patients with OSF experience a severe burning sensation in their mouths after ingesting spicy food. Finally, the patients' abilities to open their mouths become limited and their oral mucosae become hardened; moreover, they

have poor wound healing, and their cheeks and lips become tightly held against their teeth.[3,4]

RISK FACTORS

Immunologic causes (inflammation and autoimmunity) contribute to OSF, along with nutritional factors (vitamin B, C, and iron deficiency), carcinogenic causes (chewing tobacco and betel nut), alcohol, consumption of spicy food, epigenetic regulation, and genetic predisposition. Overconsumption of chili-containing food irritates the oral mucosa that may cause an inflammatory response to induce OSF. However, in Mexico and America where chili is widely used, OSF is not found. Regarding nutritional deficiency, OSF patients show significantly lower levels of serum β-carotene, iron, vitamin C and, zinc in a grade dependent manner; all these factors are known to negatively affect the wound healing process. Conversely, the patients also have higher serum levels of copper that enhance the lysyl oxidase (LOX) activity of cross-linking collagen fibers and elastin. The increase in salivary copper concentration is reported to be associated with increasing clinical grade. Epigenetic alteration had been observed in Wnt inhibitory factor-1 (WIF1) and p16 genes of the buccal cells in OSF patients. Hypermethylation of these two genes also contributes to the potential malignancy of OSF.[5,6,7,8]

Current epidemiological studies and evidence indicate that betel nut chewing is one of the most significant risk factors for OSF. Unfortunately, the commercially modified areca nut is cheap, sweet, and readily available in India. Moreover, the low oral health literacy of parents and children furthers the risk of addiction in young children, which consequently increases the burden of OSF. Arecoline is the major compound in betel nut that initiates the OSF process. Low doses of arecoline enhance the cell proliferation rate, while high doses of arecoline induce total reactive oxygen species (ROS), DNA damage, and LOX activity. The ataxia-telangiectasia mutated activated DNA repair is also inhibited by arecoline. LOX is overexpressed in oral cancer and upregulated by arecoline treatment of cells.[9,10,11]

PATHOGENESIS

OSF is mainly induced by areca nut chewing in Asia. The main components of areca nut contain 31.1% phenols, 18.7% polysaccharides, 14% fat, 10.8%fiber, and 0.5% alkaloids. Arecoline is the main alkaloid that causes the pathogenesis of the OSF. Arecoline stimulates the fibroblast cells to express growth factors and cytokines that enhance the collagen deposition and repress the collagen degradation. Clinical studies reported transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), beta fibroblast growth factor (bFGF), alpha-smooth muscle actin (α-SMA), tumor necrosis factor-α (TNF-α), serum c-reactive protein, ROS level, matrix metalloproteinases (MMP), and the tissue inhibitors ofmetalloproteinases (TIMP) were expressed abnormally in OSF group.[12]

Arecoline activates the oral tissue express TNF-α that stimulates cell inflammation. Cell inflammation will activate the wound healing reaction, which decreases MMP and increases TIMP expression. This TIMP and MMP expression profile is also found in the oral tissue of OSF patients . The function of MMP is to degrade the extracellular matrix protein, and TIMP inhibits this process. This contributes to the abnormal collagen deposition on the lesion. Inflammation reaction also stimulates the cell express bFGF and TGFβ-1. Continuously overexpressing bFGF in oral cells contributes to the collagen deposition disorder in OSF. TGFβ-1 stimulates fibroblasts to transform to myofibroblasts, which are mainly responsible for collagen production and wound contraction. Normally, myofibroblasts undergo apoptosis after finishing the mission of wound healing. However, this mechanism is disrupted in OSF. Arecoline also increases the ROS level in OSF patients' serum. Serum ROS attacks the structure of the blood vessels in endothelial cells, induced cell senescence, and DNA double-stranded breaks. The decrease in blood flow around the oral mucosa finally causes one of the pathological symptoms - epithelial atrophy. The cell inflammation reaction and ROS attack stimulate the cell to activate the TGF-β signaling pathways. The TGF-β signaling is responsible for ceasing the cell cycle and promoting apoptosis in the unrepaired damage cells while the cells are damaged by stimulants. TGF-β also activates the downstream gene, CTGF, expression to promote the fibroblast-mediated production of extracellular matrix deposition.[13]

In addition, copper participates in the cross-linking of collagen. It enhances the hardness of the oral submucosa tissue and exacerbates the limitation of mouth opening and trismus. The commercial areca nut was reported to contain a significantly higher level of copper than the raw areca nut. Higher serum copper was also found among OSF patients and was deemed as one of the factors that induce OSF.

TREATMENT

- DRUG - Corticosteroids, such as hydrocortisone, triamcinolone, dexamethasone, and betamethasone, as well as anti-inflammatory cytokines, such as interferon-gamma (IFN-γ) , ameliorate inflammation and decrease collagen formation. Enzymatic drugs, such as collagenase, hyaluronidase, and chymotrypsin, have been used in OSF treatment.[14]
- MOUTH EXCERCISING DEVICE - Therapeutic conventional exercise is a commonly used and non-invasive treatment method for patients with OSF. The devices can be prefabricated like EZBite or custom-made like an oral stent. At present, most devices are designed for vertical oral movement. The devices developed by P. G.

Pati and S. P. Patil in 2012 squeeze/stretch the cheek to increase elasticity and blood circulation of the oral mucosa. Mouth exercising devices can significantly improve the mouth opening by approximately 10.5 mm and maintain these results for 12 weeks to 6 months. Other commercially available devices such as TheraBite®, Malmö, Sweden Jaw Motion, Rehabilitation System™ (TheraBite), and DynasplintTrismus System® (DTS), have been reported to increase mouth opening up to 14 mm. EZBite designed by Li et al. in 2019, provides users a clear and simple protocol and continuously trains patients to open their mouths to a certain quantitative value each time to achieve maximal interincisal opening from 15.7 to 29.7 mm.[15]

- ELECTIVE SURGERY - Surgery is required for patients with severe OSF whose mouth opening is less than 20 mm. Clinicians use scalpel blades, electrocautery, and lasers to cut the fibers that restrict mouth opening, and coronoidectomy to reconstruct soft tissue to increase mouth opening. The fat flap, nasolabial flap, tongue flap, mandibular mucoperiosteal flap, palatal flap, and platysma myocutaneousflap are used for soft tissue reconstruction. The flap must be derived from well-vascularized tissue close to the defect, with minimum donor site morbidity to prevent OSF recurrence.[16]

CONCLUSION

The prevalence of OSF and the rate of malignant transformation are different among countries. Quitting betel nut chewing is the best strategy to prevent OSF and potential malignancy. Regardless of the strategy, clinical diagnosis and treatment are still based on conservative methods. The treatment must improve the elasticity of the oral mucosa and mouth opening distance. This ensures that patients have normal oral functions like speaking and eating to improves the patient's quality of life and provides an adequate nutritional intake. High-quality clinical studies are needed to help clinicians to develop and apply molecular biomarkers and to formulate standard treatment guidelines for OSF.

REFERENCES

1. Dionne, K.R.; Warnakulasuriya, S.; Zain, R.B.; Cheong, S.C. Potentially malignant disorders of the oral cavity: Current practice and future directions in the clinic and laboratory. *Int. J. Cancer* **2015**, *136*, 503–515.
2. Chole, R.H.; Gondivkar, S.M.; Gadbail, A.R.; Balsaraf, S.; Chaudhary, S.; Dhore, S.V.; Ghonmode, S.; Balwani, S.; Mankar, M.; Tiwari, M.; et al. Review of drug treatment of oral submucous fibrosis. *Oral Oncol.* **2012**, *48*, 393–398.
3. Wang, Y.Y.; Tail, Y.H.; Wang, W.C.; Chen, C.Y.; Kao, Y.H.; Chen, Y.K.; Chen, C.H. Malignant transformation in 5071 southern Taiwanese patients with potentially malignant oral mucosal disorders. *BMC Oral Health* **2014**, *14*, 99.
4. Zhang, X.; Reichart, P.A. A review of betel quid chewing, oral cancer and precancer in Mainland China. *Oral Oncol.* **2007**, *43*, 424–430.
5. Arakeri, G.; Rai, K.K.; Hunasgi, S.; Merkx, M.A.W.; Gao, S.; Brennan, P.A. Oral submucous fibrosis: An update on current theories of pathogenesis. *J. Oral Pathol. Med. Off. Publ. Int. Assoc. Oral Pathol. Am. Acad. Oral Pathol.* **2017**, *46*, 406–412
6. Guruprasad, R.; Nair, P.P.; Singh, M.; Singh, M.; Singh, M.; Jain, A. Serum vitamin c and iron levels in oral submucous fibrosis. *Indian J. Dent.* **2014**, *5*, 81–85.
7. Wang, Y.P.; Wu, Y.C.; Cheng, S.J.; Chen, H.M.; Sun, A.; Chang, J.Y. High frequencies of vitamin B12 and folic acid deficiencies and gastric parietal cell antibody positivity in oral submucous fibrosis patients. *J. Formos. Med. Assoc. = Taiwan Yi Zhi* **2015**, *114*, 813–819.
8. Mohammed, F.; Manohar, V.; Jose, M.; Thapasum, A.F.; Mohamed, S.; Shamaz, B.H.; D'Souza, N. Estimation of copper in saliva and areca nut products and its correlation with histological grades of oral submucous fibrosis. *J. Oral Pathol. Med. Off. Publ. Int. Assoc. Oral Pathol. Am. Acad. Oral Pathol.* **2015**, *44*, 208–213.
9. Wang, T.H.; Hsia, S.M.; Shieh, T.M. Lysyl Oxidase and the Tumor Microenvironment. *Int. J. Mol. Sci.* **2016**, *18*, 62.
10. Shih, Y.H.; Chang, K.W.; Chen, M.Y.; Yu, C.C.; Lin, D.J.; Hsia, S.M.; Huang, H.L.; Shieh, T.M. Lysyl oxidase and enhancement of cell proliferation and angiogenesis in oral squamous cell carcinoma. *Head Neck* **2013**, *35*, 250–256.
11. Shieh, T.M.; Lin, S.C.; Liu, C.J.; Chang, S.S.; Ku, T.H.; Chang, K.W. Association of expression aberrances and genetic polymorphisms of lysyl oxidase with areca-associated oral tumorigenesis. *Clin. Cancer Res.* **2007**, *13*, 4378–4385.
12. Zhang, S.S.; Li, W.H.; Gao, Y.J.; Liu, Z.W.; Liu, L.; Tang, J.Q.; Ling, T.Y. Betel-quid and oral submucous fibrosis: A cross-sectional study in Hunan province, China. *J. Oral Pathol. Med. Off. Publ. Int. Assoc. Oral Pathol. Am. Acad. Oral Pathol.* **2012**, *41*, 748–754.
13. Cai, X.; Yao, Z.; Liu, G.; Cui, L.; Li, H.; Huang, J. Oral submucous fibrosis: A clinicopathological study of 674 cases in China. *J. Oral Pathol. Med. Off. Publ. Int. Assoc. Oral Pathol. Am. Acad. Oral Pathol.* **2019**, *48*, 321–325.
14. Tilakaratne, W.M.; Ekanayaka, R.P.; Herath, M.; Jayasinghe, R.D.; Sitheeque, M.; Amarasinghe, H. Intralesional corticosteroids as a treatment for restricted mouth opening in oral submucous fibrosis. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* **2016**, *122*, 224–231.
15. Patil, P.G.; Patil, S.P. Novel mouth-exercising device for oral submucous fibrosis. *J. Prosthodont.* **2012**, *21*, 556–560.
16. Kholakiya, Y.; Jose, A.; Rawat, A.; Nagori, S.A.; Jacob, S.; Roychoudhury, A. Surgical management of oral submucous fibrosis with "Seagull-nasolabial flap" combined with short-term oral pentoxifylline for preventing relapse. *J. Stomatol. Oral Maxillofac. Surg.* **2020**.