World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

Oral submucous fibrosis: A review on current treatment approaches

Preetika S [1], Indhuja V [1] and Sowmya C [2,*]

[1] *Department of Pharmaceutics, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai-600116.*
[2] *Department of Pharmaceutics, Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai - 600116.*

World Journal of Biology Pharmacy and Health Sciences, 2023, 13(02), 157–162

Publication history: Received on 27 December 2022; revised on 07 February 2023; accepted on 09 February 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.2.0088

Abstract

Oral submucous fibrosis (OSF) is caused by aberrant collagen deposition in the oral mucosa. A chronic, creeping, scarring disease of the oral cavity often involving the pharynx and upper oesophagus is how it's been described for centuries. It is the most dangerous oral premalignant condition and evolve into malignant tumours in 1.5% to 15% of cases. It is found primarily in India, Pakistan, Sri Lanka, and Bangladesh. Submucous fibrosis, ulceration, xerostomia, a burning feeling, and a restricted opening of the mouth are some of the signs and symptoms to look out for. A patient's quality of life is severely affected by all of these factors. Chewing on areca nuts is the most significant source of danger. Efforts to improve management have been ongoing due to the disease's high mortality and high malignant transformation rate, respectively. Understanding the precise involvement of etiological agents in pathogenesis will aid in management and therapy methods. From a molecular standpoint, this paper provides an overview of background of OSF, including its underlying processes, diagnostic biomarkers, and therapy options. Prevention of OSF is just as crucial as rigorous therapy. For future studies to be effective, oral health literacy has to be improved among people at risk for OSF.

Keywords: Oral submucous fibrosis; Oral premalignant condition; Depapillated tongue; Areca nut product; Hyperbaric oxygen therapy

1. Introduction

OSF is an autoimmune disorder that causes scarring and the formation of scar tissue, as well as precancerous lesions in the oral mucous membranes.[1] the buccal mucosa is where it's most common. Collagen deposition above and below the oral mucosal epithelium, inflammation in the lamina propria or deep connective tissues and degenerative alterations in the muscles are all pathological hallmarks of this disease.[2] A significant burning sensation occurs in the mouth of OSF sufferers after eating spicy foods. Dry mouth, discomfort and abnormal taste sensations are just a few of the symptoms of OSF. Among the possible causes of OSF include autoimmune diseases like lupus and rheumatoid arthritis, nutritional deficiencies such low levels of vitamin B, vitamin C and iron as well as environmental variables like betel nut chewing and spicy food consumption. Occurrence of OSF is significantly increased when betel nut and tobacco are consumed jointly. It has been verified by several investigations that the combination of consuming alcohol and chewing betel nut can induce OSF. It is commonly accepted that OSF is a risk factor for oral precancer. According to estimates, the prevalence of OSMF in India is 0.2–2.3% in males and 1.2–4.6% in females between the ages of 11 and 60.[3] Every 7.6th OSF patient in India gets oral cancer. Symptom severity and OSF duration have been shown to be directly linked to the advancement of oral cancer. In most cases, oral cancer develops 3–16 years following the initial diagnosis of OSF.[4] unfortunately, there are no clinically viable treatments for OSF.

* Corresponding author: Sowmya C

2. Current status of the OSF in India

In addition to being extremely lethal, oral cancer is one of the most debilitating and disfiguring forms of the disease. Tobacco usage, whether it's smoked or chewed, is the most common cause of this cancer, which affects 30% to 40% of people in India.[5] More than a quarter of all adults (29.6 percent of men and 12.8 percent of women) use smokeless tobacco, according to a recent survey. Gutkha is the generic name for an Indian smokeless tobacco with a high content of carcinogens, commonly referred to as gut. More than half of India's population, 53.9 million men and 11.1 million women, live in rural areas while 16.5 million live in cities, all of whom eat gutkha. Smokeless and smoked tobacco use decreased in India between 2009 and 2016, according to Shraddha Joshi of FnBnews.com. As far as concerns concerning gutka are concerned, they remain. Despite the fact that the Centre has banned the sale of gutkha, the reality on the ground is very different. Gutkha production is still rife with illegal, unlicensed activity, despite numerous restrictions enacted by various countries. Oral cancer is the leading cause of death in India, due to a rise in the usage of gutkha. In addition to tobacco, areca nut lime, and catechu, gutkha's main carcinogens are found in its ingredients. North India's Uttar Pradesh state has a high rate of oral cancer because of the widespread usage of smokeless tobacco products like pan and gutkha.

Tobacco chewing and pan masala use are very common in the scheduled tribe (ST) community, according to a survey conducted by Rani et al. While areca nut chewing is a major health danger in rural Tamilnadu, S. Palliyal's (2017) study published in the Annals of Oncology found that oral cancer is primarily an issue among the Paniyan tribes of Wayanad (Kerala) due to betel nut consumption, which was reported by Gunaselan Rajan. Oral leukoplakia and oral submucous fibrosis are both caused by the widespread consumption of gutka/betelnuts in tribal societies. As a premalignant illness, oral submucous fibrosis (OSF) accounts for a large share of the morbidity among individuals. In addition, squamous cell carcinoma, an aggressive variety, can be lethal (1.5-15 percent of the time).[6] Ulceration, xerostomia (a dry mouth condition), a burning sensation, and a limited range of motion are all signs and symptoms of this condition. OSF is more common in some ethnic groups than others, and it's tightly linked to things like nutrition, lifestyle, and culture. There are more than a million OSF patients in India alone, but the condition is also seen in Taiwan and other Asian countries as well. As a result of South Africa's large Indian population, there are a large number of OSF sufferers in the country. WHO estimates that there are more than 5 million OSF sufferers worldwide. While OSF is more common in women in India than males, this is not always the case in other parts of the world. The patients range in age from 20 to 40 years.

Alkaloids from the fruit of the Areca nut promote collagen production and so cause submucous fibrosis in the tissues.[7] Tobacco and areca nut consumption exacerbate this disease. Each stage of OSF's evolution can be summarized as follows: As the disease progresses to stage IV, there is a loss of cheek puffiness, tongue and mouth fibrosis that restricts tongue motion and causes mucosal depapillation and blanching. The prevention of OSF becoming malignant is dependent on the early discovery and treatment of the condition. Our goal here is to identify successful molecular techniques for OSF diagnosis and treatment by analyzing the current literature on the disease's pathology, molecular diagnostics, and clinical treatment.

2.1. Symptoms and Mechanisms of Disease

The pathophysiology of oral submucous fibrosis is unknown, however it is thought to be a complex condition caused by areca nut chewing, chili consumption, hereditary factors, immunologic mechanisms, and dietary deficits.

Symptoms of OSF include chewing betel nut, which is the primary source of these symptoms. Several epithelial changes, rete-peg forms, and dense bands of collagen fibers in the sub epithelium characterize the histology of OSF.[8] From atrophy to hyperplasia and dysplasia, epithelial changes can be seen at various phases of OSF. Epithelial-mesenchymal transition (EMT) is favored by a shift in epithelial compliance because of increased connective tissue fibrosis (EMT).[9]Initial signs of OSF include ulceration, xerostomia, a burning feeling, and a limited capacity to open the mouth. They disrupt the patient's normal routine and may even lead to further problems for the patient. To repair wounds, myofibroblasts transform into contractile and secretory cells that create components of the ECM and secrete cytokines after tissue injury. A pathological fibrosis can develop if collagen or other ECM proteins build up in an excessive amount. Many investigations have shown that OSF is caused by a malfunction in collagen homeostasis, with excessive production and decreased clearance. These changes in collagen metabolism can be attributed to the consumption of betel nut. Molecules of alkaloid, flavonoid and copper are found in betel nuts.[10] In the mouth, all of these disrupt ECM equilibrium. Most people who chew betel nut also use cigarettes or drink alcohol in some form. OSF pathogenesis is exacerbated by both tobacco and alcohol use, according to research.

3. Diagnosis and methodology to diagnose the OSF

The symptoms and clinical features of OSF are taken into consideration while developing a clinical diagnosis of the condition. A biopsy needs to be performed in order to confirm the diagnosis and eliminate the possibility of dysplasia or cancer.

In the clinical setting, OSF patients will exhibit a blanching of the oral mucosa that is dull and resembles marble. In the initial phases, stomatitis symptoms such as erythematous mucosa, vesicles, mucosal ulcers, blotchy melanotic mucosal pigmentation, and mucosal petechiae may be noted.[11] As the condition progresses, it is possible to feel fibrous bands that are both vertical and circular in the buccal mucosa and all over the pericommissural region. As a result of the bands that run through the blanched mucosa, the mucosa may appear to have an uneven or marbled look. In advanced stages of the disease, symptoms such as difficulty opening the mouth (trismus), a sinking in of the cheeks that is disproportionate to the patient's age, a stiff and small depapillated tongue, a blanched floor of the mouth, fibrotic gingival tissues, a stiff soft palate with reduced mobility and a shrunken bud-like uvula, and atrophic and blanched tonsils can be observed. There is a possibility that more than one fourth of affected individuals also have leukoplakia. The buccal mucosa is the intraoral location that is affected the most frequently by OSF, followed by the lip and the tongue. However, OSF can affect any intraoral site.

Primary prevention at the population and individual levels must be enhanced, as with other lifestyle-related disorders. While it is impossible to detail all of the different measures here, OSF's strategy includes public education on the hazards of areca nut and tobacco use, as well as legislation restricting the sale of gutkha and similar items. A few of Indian states have been able to achieve this result. Gutkha has been outlawed in 24 Indian states and 5 Union Territories since May 2013, when the Food Safety and Regulation (Prohibition) Act 2011 came into effect.[12] The state's public health department, the Food and Drug Administration and the police all work together to enforce the ban. The Supreme Court and other law enforcement agencies are continuously pursuing the criminal sale of gutkha, despite a considerable decrease in legal purchases. A cure for OSF is impossible because many patients are diagnosed too late, despite efforts to enhance OSF management. Consequently, early diagnosis is critical. OSF is diagnosed clinically and it is confirmed by histology. Major symptoms include hypovascularity, which causes blanching of the oral mucosa, discoloration of teeth and gingiva, and trismus. The majority of OSF sufferers also use cigarettes and an areca nut product, may consume excessive amounts of alcohol and may engage in drug misuse of various kinds. They are frequently malnourished. As a result, co-morbid conditions such as metabolic syndromes, pulmonary, gastrointestinal/liver, and cardiovascular disorders are common among these patients. Patients can go to either a primary care physician (PCP) or a dentist, depending on the severity of their primary complaints. For diagnosis and therapy, oral signs and symptoms may be the focus of a dentist's examination and treatment plan. Because oral health is often overlooked by primary care physicians (PCPs) when patients come in, the focus of management is likely to be more general. A multidisciplinary team is rarely used to treat these individuals in most countries. We propose an inter-professional approach that may raise the rate of early detection of OSF and possibly malignant disorders/OSCC, with integrated management of both oral and systemic symptoms, increasing long-term prognosis, lowering pain and improving quality of life.

4. Current Treatment Approaches of OSF

Surgical and non-surgical procedures, including molecular approaches, are used in the majority of cases. Using a combination of physical therapy, medication, and natural chemical cures, are the treatment options for OSF.

4.1. Physical therapy

Decompression sickness, gas gangrene, and carbon monoxide poisoning can all be treated with hyperbaric oxygen therapy. HBOT involves placing the patient in a hyperbaric chamber with an oxygen pressure that is greater than the surrounding atmosphere. First used for this purpose in 1988, HBOT has since become a vital part of the treatment of periodontal disease. It was recently announced that HBOT is being used in OSF. Increased fibroblast apoptosis and decreased fibroblast activity can be attributed to HBOT's ability to reduce IL-1 and TNF- production. Proinflammatory cytokines such as IL-1, IL-6, and IL-10 are reduced with HBOT. Oxygenation in all tissues is increased, while the formation of reactive oxygen species such as E-SOD and GPx is inhibited. OSF can be treated with HBOT since it suppresses fibroblast activity and has anti-inflammatory and antioxidant qualities.[13]

4.2. Treatment with Medication

Anti-inflammatory and extracellular matrix breakdown are the primary goals of OSF medication therapy. Dexamethasone, methylprednisolone, and betamethasone are synthetic glucocorticoid medications. Synthetic

corticosteroids can dramatically enhance mouth opening and relieve the burning feeling in OSF by injecting them intralesionally into the affected area.[14] hyaluronan and collagen are degraded by chymotrypsin and hyaluronidase, two proteolytic enzymes. An anti-inflammatory effect is achieved by blocking glucocorticoid-induced inflammation mediators. Fibroblast growth and collagen deposition are also inhibited. Corticosteroids are often used in conjunction with these drugs in the treatment of OSF.[15] Xanthine derivative pentoxifylline is predominantly employed for the relief of muscle discomfort in humans.[16] Human monocytes treated with lipopolysaccharide (LPS) produce less TNF-, which is a pro-inflammatory cytokine, and less leukotriene, which is an anti-inflammatory cytokine, which is inhibited.[17] This medication reduced the burning sensation in OSF by improving mouth opening. It also made swallowing and speaking easier. Colchicine has been used to treat joint swelling since 1500 BC. Medical usage was allowed in 1961. To reduce inflammation, it inhibits neutrophil activation in order to prevent their migration to the affected area and to restrict IL-1 activity. Colchicine's ability to treat OSF was first documented in 2013. Hyaluronidase injections into each buccal mucosal lesion were given to OSF patients once a week, with 0.5 mg of oral colchicine taken twice a day.[18] There were noticeable improvements in mouth opening and histological markers by week two of treatment. 0.5 mL lignocaine hydrochloride once weekly increased mouth opening and decreased burning in patients with grade II OSF after 12 weeks with the aforementioned dosages.[19]

4.3. Remedies Made from Natural Ingredients

Nutritional supplements, a diet rich in minerals, such as tomatoes, carrots, and watermelons, green vegetables, and green tea are commonly suggested for OSF patients, albeit there are few studies demonstrating their direct usefulness. Turmeric is a powerful antioxidant with numerous medicinal properties. It has been reported to reduce histamine while increasing the synthesis of natural cortisol, hence lowering free radical damage and alleviating inflammation.[20] Ginger butter resin, ginger butter, and turmeric extract have been demonstrated to be beneficial for OSF. The systemic mixed local form is more effective at treating OSF than the systemic form alone. Lycopene, a red carotenoid found in tomatoes, is a potent antioxidant. When the treatment of lycopene and curcumin in OSF patients was compared, it was discovered that lycopene is more beneficial in enhancing mouth opening and lowering the burning sensation.[21] In summary, it is recommended that OSF patients consume more natural foods with anti-inflammatory and antioxidant characteristics, such as honey, fruits, and green vegetables, and pay attention to their nutritional balance.

4.4. Surgical procedures:

For advanced and severe patients, surgery has become the therapy of choice. Many surgical procedures have been published in the literature, including cauterization with a knife or laser resection of the fibrous band, followed by graft reconstruction with medium thickness skin flap, bilateral nasolabial groove flap or buccal fat pad. However, the recurrence rate following surgery is extremely significant. Furthermore, surgical treatment of patients with advanced OSF can result in a number of problems, including partial or total flap necrosis, hair growth in the mouth, scar outside the mouth, and wound dehiscence.[22] To limit the incidence of complications, surgeons should exercise due care during the operation, and patients should be reminded to give up bad habits, alter unhealthy lifestyles, boost immunity, consume more green vegetables, red fruits, and trace elements and so on.

5. Conclusion

In spite of decades of research, OSF is still mostly unknown and poorly understood. Chewing betel nuts is very common among Asians. It causes structural and compositional anomalies by increasing the production and lowering the clearance of collagen, causing the body to produce more collagen and less of it. OSF detection by molecular pathology approaches focuses on biomarkers that trigger aberrant collagen deposition and involves both invasive and non-invasive investigations. A combination approach, involving investigation of genetic and epigenetic regulators with diverse habits, may be useful in better understanding the contributory elements and pathophysiology of this significant condition. For the most part, pharmacological treatments for OSF have been shown effective. Patients at risk for developing OSCC should avoid unhealthy habits like betel nut chewing and tobacco smoking and instead eat a diet rich in anti-inflammatory and antioxidant-rich foods. No meaningful improvement in care or reduction in the high rate of malignant transformation has been seen in its increasing prevalence. In underdeveloped nations, better integration of medical and dental services may minimize patients' suffering and improve their quality of life. Public education and primary prevention must be coordinated by all health care professionals.

Compliance with ethical standards

Acknowledgments

Authors are thankful to the Central Library (Hard ward Learning Centre), Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai-16.

Disclosure of conflict of interest

Authors declares no conflicts of interest between them.

References

[1] Tilakaratne, W. M., Klinikowski, M. F., Saku, T., Peters, T. J., & Warnakulasuriya, S. (2006). Oral submucous fibrosis: Review on Aetiology and pathogenesis. Oral Oncology, 42(6), 561–568. https://doi.org/10.1016/j.oraloncology.2005.08.005

[2] Peng, Q., Li, H., Chen, J., Wang, Y., & Tang, Z. (2019). Oral submucous fibrosis in Asian countries. Journal of Oral Pathology & Medicine, 49(4), 294–304. https://doi.org/10.1111/jop.12924

[3] Munde, A., Nayak, P., Mishra, S., Karle, R., Farooqui, A., Sawade, R., & Deshpande, A. (2021). Demographic and clinical profile of oral submucous fibrosis: A retrospective study. Journal of Pharmaceutical Research International, 308–317. https://doi.org/10.9734/jpri/2021/v33i56a33916

[4] Wang, L., & Tang, Z. (2021). Immunopathogenesis of oral submucous fibrosis by chewing the areca nut. Journal of Leukocyte Biology, 111(2), 469–476. https://doi.org/10.1002/jlb.3mr0521-763rr

[5] Byakodi, R., Byakodi, S., Hiremath, S., Byakodi, J., Adaki, S., Marathe, K., & Mahind, P. (2011). Oral cancer in India: An epidemiologic and clinical review. Journal of Community Health, 37(2), 316–319. https://doi.org/10.1007/s10900-011-9447-6

[6] Petter, G., & Haustein, U.-F. (2000). Histologic subtyping and malignancy assessment of cutaneous squamous cell carcinoma. Dermatologic Surgery, 26(6), 521–530. https://doi.org/10.1046/j.1524-4725.2000.99181.x

[7] Prabhu RV;Prabhu V;Chatra L;Shenai P;Suvarna N;Dandekeri S; (n.d.). Areca nut and its role in oral submucous fibrosis. Journal of clinical and experimental dentistry. Retrieved November 14, 2022, from https://pubmed.ncbi.nlm.nih.gov/25674328/

[8] Shih, Y.-H., Wang, T.-H., Shieh, T.-M., & Tseng, Y.-H. (2019). Oral submucous fibrosis: A review on etiopathogenesis, diagnosis, and therapy. International Journal of Molecular Sciences, 20(12), 2940. https://doi.org/10.3390/ijms20122940

[9] Stone RC;Pastar I;Ojeh N;Chen V;Liu S;Garzon KI;Tomic-Canic M; (n.d.). Epithelial-mesenchymal transition in tissue repair and fibrosis. Cell and tissue research. Retrieved November 14, 2022, from https://pubmed.ncbi.nlm.nih.gov/27461257/

[10] Prabhu RV;Prabhu V;Chatra L;Shenai P;Suvarna N;Dandekeri S; (n.d.). Areca nut and its role in oral submucous fibrosis. Journal of clinical and experimental dentistry. Retrieved November 14, 2022, from https://pubmed.ncbi.nlm.nih.gov/25674328/

[11] Oral submucous fibrosis (OSF) . A digital manual for the early diagnosis of oral neoplasia. (n.d.). Retrieved November 14, 2022, from https://screening.iarc.fr/atlasoral_list.php?cat=a5&lang=1

[12] Rao, N. R., Villa, A., More, C. B., Jayasinghe, R. D., Kerr, A. R., & Johnson, N. W. (2020). Oral submucous fibrosis: A contemporary narrative review with a proposed inter-professional approach for an early diagnosis and clinical management. Journal of Otolaryngology - Head & Neck Surgery, 49(1). https://doi.org/10.1186/s40463-020-0399-7

[13] Shih, Y.-H., Wang, T.-H., Shieh, T.-M., & Tseng, Y.-H. (2019, June 16). Oral submucous fibrosis: A review on etiopathogenesis, diagnosis, and therapy. MDPI. Retrieved November 15, 2022, from https://doi.org/10.3390%2Fijms20122940

[14] Shih, Y.-H., Wang, T.-H., Shieh, T.-M., & Tseng, Y.-H. (2019, June 16). Oral submucous fibrosis: A review on etiopathogenesis, diagnosis, and therapy. MDPI. Retrieved November 15, 2022, from https://doi.org/10.3390%2Fijms20122940

[15] Tilakaratne, W. M., Ekanayaka, R. P., Herath, M., Jayasinghe, R. D., Sitheeque, M., & Amarasinghe, H. (2016, April 19). Intralesional corticosteroids as a treatment for restricted mouth opening in oral submucous fibrosis. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. Retrieved November 15, 2022, from https://www.oooojournal.net/article/S2212-4403(16)30015-3/fulltext

[16] Hassan, I., Dorjay, K., & Anwar, P. (2014, October). Pentoxifylline and its applications in dermatology. Indian dermatology online journal. Retrieved November 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4228656/

[17] Matic, M., & Simon, S. R. (2004, April 20). Tumor necrosis factor release from lipopolysaccharide-stimulated human monocytes: Lipopolysaccharide tolerance in vitro. Cytokine. Retrieved November 15, 2022, from https://www.sciencedirect.com/science/article/abs/pii/104346669190484U

[18] Krishnamoorthy, B., & Khan, M. (2013, July). Management of oral submucous fibrosis by two different drug regimens: A comparative study. Dental research journal. Retrieved November 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793419/

[19] Shih, Y.-H., Wang, T.-H., Shieh, T.-M., & Tseng, Y.-H. (2019, June 16). Oral submucous fibrosis: A review on etiopathogenesis, diagnosis, and therapy. International journal of molecular sciences. Retrieved November 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6627879/

[20] Nagpal, M., & Sood, S. (2013, January). Role of curcumin in systemic and Oral Health: An overview. Journal of natural science, biology, and medicine. Retrieved November 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3633300/

[21] Gupta, N., Kalaskar, A., & Kalaskar, R. (2020). Efficacy of lycopene in management of oral submucous fibrosis- A systematic review and meta-analysis. Journal of oral biology and craniofacial research. Retrieved November 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7549120/

[22] Kshirsagar, R., Mohite, A., Gupta, S., Patankar, A., Sane, V., & Raut, P. (2016). Complications in the use of bilateral inferiorly based nasolabial flaps for advanced oral submucous fibrosis. National journal of maxillofacial surgery. Retrieved November 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5357923/