

Cancer Association of South Africa (CANSA)



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Fact Sheet on Oral Submucous Fibrosis

Introduction

Oral Submucous Fibrosis (OSF) is a chronic, complex potentially potent pre-cancerous condition characterised by juxta-epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Approximately 20% of patients may develop oral cancer.

[Picture Credit: Oral Submucous Fibrosis]

As the disease progresses, the jaws become rigid to the point that the sufferer is unable to open his/her mouth. The condition is linked to oral cancers and is particularly associated with areca nut chewing, the main component of betel quid. Areca nut or betel quid chewing, a habit similar to tobacco chewing, is practiced predominantly in Southeast Asia, India, and east Africa dating back thousands of years.



Shih, Y-H., Wang, T-H., Shieh, T-M. & Tseng, Y-H. 2019.

“Oral submucous fibrosis (OSF) is characterized by abnormal collagen deposition. It is a precancerous disorder and transforms into a malignant tumor in 1.5-15% of all cases. Symptoms include submucous fibrosis, ulceration, xerostomia, a burning sensation, and restricted mouth opening. All of these greatly interfere with patient quality of life. The present review introduces OSF from a molecular perspective and summarizes what is known about its underlying mechanisms, diagnostic biomarkers, and therapeutic interventions. In addition to the aggressive treatment of OSF, its prevention is also important. Future research should, therefore, focus on improving the oral health literacy of the patients susceptible to OSF.”

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April 2020

More, C.B. & Rao, N.R. 2019.

“Oral Submucous Fibrosis (OSMF) is an insidious, chronic, complex, crippling, debilitating, irreversible, progressive, scarring, potentially malignant and collagen metabolic disorder, induced by a known carcinogen areca nut; wherein the oral mucosa, and occasionally the pharynx and esophagus is subjected to various pathological changes with significant clinical manifestations at different stages of progression, leading to functional morbidity; and with a risk of malignant transformation in the overlying epithelium. Although the condition is mainly diagnosed based on classic clinical manifestations, the commonly used existing definition for oral submucous fibrosis is primarily based on histological features. The authors have conducted extensive clinical research studies on OSMF and intends to propose a new clinical definition as 'a debilitating, progressive, irreversible collagen metabolic disorder induced by chronic chewing of areca nut and its commercial preparations; affecting the oral mucosa and occasionally the pharynx and esophagus; leading to mucosal stiffness and functional morbidity; and has a potential risk of malignant transformation.' Thus, a new clinical definition is put forward so as to assist the academicians, researchers and clinicians in terming and grouping this disease according to its clinical and biological behaviour for its subsequent management.”

Areca Nut

The **areca nut** is the seed of the areca palm (*Areca caechu*), which grows in much of the tropical Pacific, Asia, and parts of east Africa. It is commonly referred to as *betel nut*, as it is often chewed wrapped in betel leaves (paan).

[Picture Credit: Areca Nut]



The habit has many harmful effects on health. The International Agency for Research on Cancer (IARC) concluded that chewing areca nut is carcinogenic (cancer causing) to humans. Various compounds present in the nut, most importantly arecoline, contribute to histologic changes in the oral mucosa. As with chewing tobacco, its use is discouraged.

Causes and Risk Factors of Oral Submucous Fibrosis (OSF)

A number of risk factors seem to contribute to the juxtaepithelial inflammatory disease process in the oral mucosa leading to OSF. A strong association has been observed with areca nut chewing with or without tobacco and OSF.

The other factors that are considered to be responsible are capsaicin in chilies and micronutrient deficiencies of iron, zinc and essential vitamins.

An increase in the frequency of this disease, especially among the young, has been reported in India due to the increase in the use of commercially prepared areca nut preparations without betel leaf (*pan masala*). A genetic predisposition for the development of this disease has also been reported.

The areca nut, which contains alkaloids, such as arecoline, and other chemicals, such as catechin and tannin, plays a major role by stimulating production of collagen fibres and making them less

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susceptible to the action of collagenase. It is suggested that components of the areca nut also affect gene expression in the fibroblasts leading to the production of greater amounts of normal collagen. Areca nut has been shown to have a high copper content, and chewing areca nuts for 5–30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in OSF by stimulating fibrogenesis through up-regulation of lysyl oxidase activity.

It is not altogether clear if a hypersensitivity reaction to chilies plays any role in the development of OSF. Iron deficiency anaemia, vitamin B complex deficiency, and malnutrition are implicated in the pathogenesis of OSF leading to deranged repair processes of the inflamed oral mucosa, contributing to defective healing and scarring. The resulting atrophic oral mucosa is more susceptible to the effects of areca nut and alcohol. An immunologic process and a genetic component are assumed to be involved because of reported cases in non–areca nut chewers. Increased levels of pro-inflammatory cytokines and reduced antifibrotic interferon have also been demonstrated in patients with OSF.

Ray, J.G., Chatterjee, R. & Chaudhuri, K. 2019. “Oral submucous fibrosis is a potentially malignant disorder of the oral cavity, with a high rate of malignant transformation. It is very common among habitual areca nut chewers. The pathogenesis of oral submucous fibrosis is not well established, but it is believed to be a disease of multifactorial origin, including areca nut chewing, ingestion of chilies, genetic factors, immunologic processes and nutritional deficiencies. Genetically susceptible individuals when exposed to areca nut chewing develop this disease over a variable period of time. Oral submucous fibrosis is considered to be a disease of collagen metabolism. Several genetic factors are reported but there is no consensus about the exact mechanism of disease initiation. Variations in histopathological presentation are noted among oral submucous fibrosis patients with habitual areca nut chewing in different forms and other additive agents, eg betel quid, pan masala and gutkha, together with a variety of tobacco habits. The role of epigenetic modifications, such as miRNA regulation, and DNA methylation is also being reported as part of the pathogenesis of oral submucous fibrosis. A combined approach, including analysis of genetic and epigenetic regulations with different habits, might be helpful to better understand the contributory factors and pathogenesis of this serious disorder.”

Rangaswamy, S., Chikkalingaiah, R.G., Sanjeevarayapa, P.N. & Govindraju, P. 2019.

Introduction: Oral submucous fibrosis is a chronic debilitating condition with potential for malignant transformation. Squamous cell carcinoma arising from a background of oral submucous fibrosis presents clinically as a distinct disease due to different etiopathogenesis.

Methodology: This prospective case series describes thirty cases of oral squamous cell carcinoma (OSCC) alongside oral submucous fibrosis (OSF). Patient clinical data were recorded including type and duration of habits, site of tumor, size, histological grading and nodal status.

Results: A total of 76% cases were reported in males and 24% in females. A total of 73.3% cases had a history of use of gutka of which 16% used only arecanut or gutka while the remaining used gutka along with smoking and quid habits and 26.7% cases smoked tobacco products or used smokeless tobacco. Primary site of presentation was buccal mucosa and seven cases of carcinoma at retromolar trigone (RMT) altogether accounting for 66% of the cases. 53.3% cases reported were advanced tumour T4 lesions, 10% T3 lesion, 30% reported as T2 lesions and 6.7% T1 lesion. 55% of cases showed nodal involvement of different level and 46.5% cases were NO. About 60% of cases were histologically well differentiated squamous cell carcinoma.

Conclusion: Carcinoma arising from a background of oral submucous fibrosis follows a distinct clinical presentation. Malignant transformation occurs in younger age group and with better histological grading.

Muthukrishnan, A. & Warnakulasuriya, S. 2018.

“Smokeless tobacco (SLT) use has many oral effects including oral cancer, leukoplakia and erythroplakia, oral submucous fibrosis (if mixed with areca nut), loss of periodontal support (recession) and staining of teeth and composite restorations. This review was aimed to provide information to identify oral lesions that occur due to the use of smokeless tobacco so that effective interventions can be undertaken to reduce morbidity and mortality from the use of SLT.”

Oral Submucous Fibrosis (OSF) Incidence in South Africa

The outdated National Cancer Registry (2014) does not provide information regarding Oral Submucous fibrosis.

A review of research related to oral submucous fibrosis (OSF) among South Africans of Indian descent shows a certain uniqueness compared to other countries. In South Africa the betel habit is more common among women, only 60% of chewers prefer the betel quid while the rest like the nut by itself, the majority of chewers prefer the baked (black) nut variety and a minority add tobacco to their chew. This pattern reflects in the distribution of OSF and the practice of the habit by OSF subjects. Compared to chewers without OSF, OSF subjects are younger and have shorter histories of chewing. Yet the profile of systemic diseases were similar among subjects with and without OSF.

The habit as practised in South Africa also determines the pattern of oral squamous carcinomas. They are more common in women, with buccal mucosa cancers being the most frequent. The latter are commonly found in subjects not using any tobacco, indicating the carcinogenicity of the areca nut. It was also shown that oral cancer can develop in chewers without an intermediate precancerous OSF phase. A follow-up of OSF cases after cessation of the habit revealed that once present the disease is permanent. An analysis of cultured OSF fibroblasts demonstrated a permanent shift to larger cells theoretically capable of producing larger amounts of collagen. Thus the agents in the nut could be the initiators of the disease and its permanent character the result of a phenotypic alteration in cells from changes in gene expression.

(van Wyk, 1997).

Signs and Symptoms of Oral Submucous Fibrosis (OSF)

The first symptom of oral submucous fibrosis is a burning sensation in the mouth especially when eating spicy food, sometimes also with small blister formation. The mouth may feel dry with ulcers.

On examination, even at an early stage, the oral mucosa looks white in a marble-like pattern, either diffusely throughout the mouth or in localised areas, or in a netlike pattern.

In later stages fibrosis develops:

[Picture Credit: Mouth Opening Reduced]



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- mouth cannot be opened as wide as normal, affecting eating and swallowing, speaking and dental hygiene.
- tongue becomes smooth, white and cannot move easily.
- the cheeks feel thick and firm and cannot 'puff out'.
- lips become rubbery and thick with an elliptical shape.

In very severe cases, the fibrosis extends to the soft palate, throat and oesophagus. The uvula may shrink and become distorted in shape. Difficulty may occur with swallowing and the Eustacian tubes to the ear may be blocked, affecting hearing.

Although most of the inside of the mouth can become fibrotic, the gums are uncommonly affected. Involvement on just one side of the mouth has been reported when the betel quid is habitually held in one specific site. The pattern of involvement is also affected by whether the quid is swallowed after chewing, or spat out. Swallowing exposes the soft palate, throat and oesophagus to the betel quid and therefore these areas at the back of the mouth are more likely to be affected than in those who spit the quid out. Those who spit it out are more likely to have involvement of the lips and areas towards the front of the mouth.

There is an increased risk of developing squamous cell carcinoma in the thinned oral mucosa. The risk has been estimated to be as high as 1 in 5 in some reports.

Arakeri, G., Aliabab, A., Nagaraj, M., Hunasgi, S., Patil, S. Hale, B., Merckx, M.A.W., Gomes, C.C., Gomez, R.S. & Brennan, P.A. 2019.

BACKGROUND: Despite much research, there is a lack of a definite protocol or method for documenting oral submucous fibrosis (OSMF) site presentation. In this study we propose a new potential oral mapping (OM) method and evaluated its use in recording OSMF affected mucosal sites.

METHODS: 50 OSMF patients were evaluated by 15 primary care dental practitioners using both, a conventional subjective recording method and a new OM method, to document the degree of involvement of affected oral mucosa with a crossover study design. Mann-Whitney test (Non-parametric test) was used to make comparison between groups to determine any significant differences between the two identification methods. Wilcoxon tests were used to evaluate any significant differences in the difficulty in identification of two methods.

RESULTS: There was a low agreement between the two methods used to detect OSMF in affected mucosal surfaces (p-value <0.0001). More lesions were identified using the proposed OM method and less discrepancy was found among dental practitioners. A difference in difficulty of OSMF documentation was found (Wilcoxon $z = 3.615$, p-value <0.001), with the proposed OM method found to be easier.

CONCLUSION: The proposed OM method appears to be useful for documentation, can easily be adapted in clinical practice and effectively administered in clinical research. Additionally, it could be a useful tool to helping to maintain an OSMF database. This article is protected by copyright. All rights reserved.

Diagnosis of Oral Submucous Fibrosis (OSF)

The differential diagnosis for Oral Submucous Fibrosis includes Lichen Planus, Scleroderma, and Squamous Cell Carcinoma. The conclusion that an individual may present with Oral Submucous

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Fibrosis may be achieved using several different modalities to confirm a diagnosis. In a study conducted by Chiu *et al.*, A total of 296 subjects were recruited, including 123 Oral Submucous Fibrosis patients whose condition had not yet progressed to malignancy as well as 173 betel quid chewers who did not demonstrate existing Oral Submucous Fibrosis. The subjects were given a questionnaire and had their maximal mouth opening recorded. The distance between upper and lower incisor edges was measured with the following results.

Normal mouth opening in healthy individuals ranges from 40-50mm. According to the questionnaire subjects with a maximum mouth opening of less than 35mm complained of trismus (87.3%), burning sensation (76.0%), and xerostomia (72.25%). Subjects with a maximum mouth opening greater than 35mm complain of burning sensation (68.2%) followed by trismus (54.5%) and xerostomia (54.5%). Although this is not a confirmation of the disease, it does provide researchers with better understanding of its pathogenesis. A biopsy is the ultimate determining factor and should be performed to rule out Squamous Cell Carcinoma (Vanessa M Cook).

Treatment of Oral Submucous Fibrosis (OSF)

Medical Treatment - the treatment of patients with oral submucous fibrosis depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with oral submucous fibrosis present with moderate-to-severe disease. Moderate-to-severe oral submucous fibrosis is irreversible. Medical treatment is symptomatic and predominantly aimed at improving mouth movements. Treatment strategies may include the following:

- **Steroids:** In patients with moderate oral submucous fibrosis, weekly submucosal intralesional injections or topical application of steroids may help prevent further damage.
- **Placental extracts:** The rationale for using placental extract in patients with oral submucous fibrosis derives from its proposed anti-inflammatory effect, hence, preventing or inhibiting mucosal damage. Cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human placental extract (Placentrex) has shown marked improvement of the condition.
- **Hyaluronidase:** The use of topical hyaluronidase has been shown to improve symptoms more quickly than steroids alone. Hyaluronidase can also be added to intralesional steroid preparations. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone.
- **IFN-gamma:** This plays a role in the treatment of patients with oral submucous fibrosis because of its immunoregulatory effect. IFN-gamma is a known antifibrotic cytokine. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with oral submucous fibrosis, and intralesional injections of the cytokine may have a significant therapeutic effect on oral submucous fibrosis.
- **Lycopene:** Newer studies highlight the benefit of this oral nutritional supplement at a daily dose of 16 mg. Mouth opening in 2 treatment arms (40 patients total) was statistically improved in patients with oral submucous fibrosis. This effect was slightly enhanced with the injection of intralesional betamethasone (two 1-mL ampules of 4 mg each) twice weekly, but the onset of effect was slightly delayed.
- **Pentoxifylline:** In a pilot study, 14 test subjects with advanced oral submucous fibrosis given pentoxifylline at 400 mg 3 times daily were compared to 15 age- and sex-matched diseased control subjects. Statistical improvement was noted in all measures of objective (mouth

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opening, tongue protrusion, and relief from fibrotic bands) and subjective (intolerance to spices, burning sensation of mouth, tinnitus, difficulty in swallowing, and difficulty in speech) symptoms over a 7-month period. Further studies are needed, but this could be used in conjunction with other therapies.

The role of these treatments is still evolving. The US Food and Drug Administration has not yet approved these drugs for the treatment of oral submucous fibrosis.

Surgical treatment - is often indicated in patients with severe trismus (means being unable to open the mouth completely. It can be caused by muscle, nerve or joint damage) and/or biopsy results revealing dysplastic or neoplastic changes. Surgical modalities that have been used include the following:

- Simple excision of the fibrous bands: Excision can result in contracture of the tissue and exacerbation of the condition.
- Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy: Trismus (means being unable to open the mouth completely. It can be caused by muscle, nerve or joint damage) associated with oral submucous fibrosis may be due to changes in the temporalis tendon secondary to oral submucous fibrosis; therefore, skin grafts may relieve symptoms.
- Nasolabial flaps and lingual pedicle flaps: Surgery to create flaps is performed only in patients with oral submucous fibrosis in whom the tongue is not involved.
- Use of a KTP-532 laser release procedure was found to increase mouth opening range in 9 patients over a 12-month follow-up period in one study.
- ErCr:YSGG laser fibrotomy, performed under a local anaesthesia, may be a useful adjunct in managing oral submucous fibrosis.

Thukral, H., Roy, Chowdhury, S.K. & Nagori, S.A. 2018.

“The aim of our study was to evaluate the effectiveness of buccal fat pad (BFP) in the management of oral submucous fibrosis(OSMF). Retrospective records of 30 patients of OSMF treated with BFP with atleast a year of follow-up were analyzed. Patients were divided into groups based on the stages of OSMF. Surgical management consisted of resection of fibrous bands, bilateral temporalis myotomy, and coronoidectomy followed by grafting with BFP. There were 17 patients of stage III (mouth opening 16-25 mm) and 13 patients of stage IV OSMF (mouth opening less than 16 mm). The mean mouth opening of stage III group pre-operatively was 19.94 ± 2.19 mm which increased to a mean of 35.12 ± 5.69 mm ($p < 0.0001$). For patients with stage IV OSMF, the mouth opening increased from a pre-operative of 10.23 ± 4.07 mm to a post-operative of 31.46 ± 6.78 mm ($p < 0.0001$). No intra-operative complications were noted in any patient. Relapse was seen in 1 patient (5.8%) of stage III while 3 patients (23.07%) had relapse in stage IV group. Our results indicate that BFP is a good flap owing to its benefits which are easy to harvest and entails minimal morbidity for management of OSMF.”

Al-Maweri, S.A., Ashraf, S., Lingam, A.S., Algutaibi, A., Abdulrab, S., Alaizari, N. & Halboub, E. 2018.

“The management of oral submucous fibrosis (OSF) is quite challenging, and as yet, no effective therapy is available for its management. The present systematic review and meta-analysis sought to assess the effectiveness of aloe vera in alleviating pain and clinical signs of OSF. A comprehensive search in PubMed/Medline, Scopus, and Web of Science databases was conducted to identify the relevant randomized clinical trials. RevMan 5.3 software was used for data analysis. Six randomized

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controlled trials fulfilled the inclusion criteria. The results of meta-analysis showed statistically significant differences between aloe vera and control groups in alleviating pain/burning sensation at the end of the first and second month, in favor of aloe vera, but no significant differences were found at the end of the third month. With regard to objective clinical outcomes, no statistically significant differences were found between the groups. Aloe vera has a promising effect in reducing pain/burning sensation and clinical improvement in patients with OSF. However, owing to the marked heterogeneity of the included studies, conducting well-designed trials with long follow-up periods, standardized outcome measures and adequate sample sizes are warranted.”

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DermNet NZ

<http://www.dermnetnz.org/site-age-specific/oral-fibrosis.html>

IARC Screening Group

http://screening.iarc.fr/atlasoral_list.php?cat=A5&lang=1

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