

## ORAL SUBMUCOUS FIBROSIS-A REVIEW ON ITS ETIOPATHOGENESIS

<sup>1</sup> Jagathesh P  
<sup>2</sup> Christeffi Mabel R

<sup>1</sup> Reader  
<sup>2</sup> Reader

<sup>1</sup>Department of Oral Medicine and Radiology, Narayana Dental College, Nellore, Andhra Pradesh, India.

<sup>2</sup>Department of Oral Medicine and Radiology, Chettinad Dental College and Research Institute, Chennai, Tamilnadu, India.

**ABSTRACT:** The chains of habit are generally too small to be felt until they are too strong to be broken". HABIT' is an automatic pattern of behavior in reaction to a specific situation, may be inherited or acquired through frequent repetition. Betel quid chewing is one such habit, and it is an ancient practice common in many countries of Asia and among migrated Asian communities in Africa, Europe and North America. Oral submucous fibrosis is a progressive disease of the oral and pharyngeal mucosa sometimes involving the esophagus. This manuscript attempts to review the etiopathologies and various treatment modalities available.

**KEYWORDS:** OSMF, betal nut, submucous fibrosis, Blanching.

### INTRODUCTION

Oral Submucous Fibrosis is a chronic, precancerous condition affecting the South and South East Asian population especially those in the Indian subcontinent due to betel quid chewing<sup>1</sup>. Betel Quid consists of a mixture of areca nut, slaked lime, catechu, and frequently, various condiments (such as cardamom seeds, aniseed or gambir) are wrapped in a betel leaf (Piper betel). The practice of chewing areca nut in a quid is at least two millennia old in India owing to the cultural heritage<sup>2</sup>. It is completely accepted in many societies of India. Women are also encouraged to use it particularly during pregnancy considering the good effects (enhances digestion) of betel leaf. Various authors have recently reported the use of betel nut as an etiological factor in the development of oral submucous fibrosis<sup>3,4,5</sup>.

Oral Submucous Fibrosis is defined by Pindborg et al 1966 as an "insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx occasionally preceded by and/or associated with a juxta-epithelial inflammatory reaction followed by a fibroelastic transformation of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat<sup>6</sup>. Now there is a convincing epidemiological evidence implicating areca nut as the causative factor in the pathogenesis of this disorder<sup>7</sup>. Areca nut (which is the endosperm of the fruit of the areca catechu tree) is the main ingredient of the quid and Gupta et al has reported in his paper that it is the fourth most commonly used psychoactive substance in the world<sup>8</sup>. Arecanut has psychotropic and antihelminthic activity and known to have powerful parasympathetic properties producing euphoria and counteracting fatigue<sup>9</sup>. Since people chew pan masala at a comparatively younger age and it requires only a shorter duration of chewing (a prodromal period of 2 to 5 yrs) to precipitate submucosal fibrosis, there is an

increased risk of developing malignant changes at a younger age<sup>10</sup>. The youngest age reported with this condition is a 4yr old immigrant girl in Canada who had been chewing areca nut since the age of 2<sup>11</sup>.

### Evolution of terminologies

Several authors coined various terminologies of this condition. These terminologies are summarized by Abrol (1977)<sup>12</sup>.

<b>Lal , 1953</b>	Diffuse Oral submucous fibrosis
<b>Su, 1954</b>	Idiopathica scleroderma of mouth,
<b>Desa, 1957</b>	Submucous fibrosis of the palate and cheek .
<b>George, 1958</b>	Submucous fibrosis of palate and mucous membranes
<b>Rao, 1962</b>	Idiopathic palatal fibrosis
<b>Behl, 1962</b>	Sclerosing stomatitis
<b>Pindborg and Sirsat , 1966</b>	Oral Submucous Fibrosis
<b>Abrol et al, 1977</b>	Idiopathic oral fibrosis.

**Etiopathogenesis of OSMF:** Areca nut (often erroneously referred to as betel nut) is the endosperm of the fruit of the Areca catechu tree. The fruit is orange-yellow in colour when ripe. The fibrous pericarp is removed from the seed or endosperm, which is then used fresh, after sun drying

or in a cured form. Areca nut contains tannins (11.4 to 26.0%) of which gallic acid (18.03%) and D-catechol (0.4%) are important. Arecoline is the most common alkaloid (0.15-0.67%); other contents include arecaidine, guvacine, isoguvacine, arecolidine and guvacoline.<sup>13</sup> showed that arecoline and its hydrolysis products, arecaidine dose-dependently stimulate human buccal mucosa fibroblasts to proliferate and synthesize collagen. Other substances comprises of fats, carbohydrates, proteins, and mineral matter. In India, areca nut is chewed by itself, in the form of various areca nut preparations. Chewing areca nut is traditionally practiced in South East Asia and among Indians living abroad.

**Various Hypotheses about Areca Nut as the Main Etiologic Factor:** Arecoline, an alkaloid in the areca catechu, has been shown to stimulate collagen synthesis by 170%<sup>14</sup>. In addition, Tannins and Catechins can cross-link collagen noncovalently, rendering it resistant to degradation by mammalian fibroblasts collagenase and may further enhance the fibrosis<sup>15</sup>. In a study, a clear dose-dependant relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of OSMF. The OSMF patients who were chewing gutkha and other products for less than 5 minutes in duration and less than 5 pouches (1 pouch = about 3.5 gram) per day in quantity mostly developed grade I of OSMF. On the other hand OSMF patients who were chewing gutkha and other products at a rate of 10 pouches per day with a chewing period of more than 5 minutes developed more severe OSMF. In another study, it has been postulated that frequency of chewing rather than duration was more directly responsible for producing OSMF.<sup>[16,17]</sup> also agreed that frequency of taking gutkha is directly related to the severity of OSMF but duration of using has no effect. Maher et al. 1994 in their study from Pakistan also reported that frequency of taking areca nut and tobacco quid has a significant relation with the severity of OSMF but duration has no relation even if the patient takes gutkha throughout his life, the style of chewing gutkha and other products have very significant relation with the severity of OSMF<sup>18</sup>. It is evident that most of the patients who chewed gutkha and spitted it out after keeping for few minutes, developed mostly grade I OSMF.

Some workers have mentioned that there exists a strong relation of OSMF with the location of placement of the quid in different regions of mouth, which are affected by different styles of chewing<sup>19</sup>. Some literature could be found which describes that the severity of the disease is associated with keeping longer duration of areca nut and tobacco quid in the buccal vestibule<sup>20</sup>. However, in the data of the present histopathological and epidemiological study, severity of OSMF has been found in mostly the cases, which chewed the gutkha and other products and swallowed it or kept in the buccal vestibules for longer period. It is possible that as areca nut has high alkaloid arecoline and tobacco ingredients like nitrosoamine, which are, absorbed more in the patients who keep it for longer

periods in their buccal vestibules or swallow it, have more severity of the disorder.

Commercially freeze dried products such as pan masala, gutka, and mawa have higher concentrations of areca nut per chew and appear to cause OSF more rapidly than self-prepared conventional betel quid, which contains smaller amounts of areca nut. Another fact is that the betel leaf (of the quid) contains ant mutagenic substance such as beta-carotene and hydroxycharicol, which may afford some protection to the oral mucous membrane against some harmful alkaloids of areca nut, this explains smaller number of cases developing OSF with quid chewing than with areca nut alone<sup>21</sup>. Interestingly, it was suggested that the addition of slaked lime to areca nut in betel quid hydrolysis arecoline to arecaidine. This means that the hydrolysis of arecoline could occur in the saliva as well as in fibroblasts. It was suggested that the inflamed oral mucosa has enhanced permeability to arecoline and arecaidine<sup>22</sup>. Studies have shown the presence of high copper content in areca nut products. Chewing 3gm of pan parag for 30 minutes increased the concentration of copper in whole mouth saliva, peaking after 10-20 min and dropping to control values 10 minutes after chewing stopped. Support of the areca nut theory comes from studies, which demonstrate that inorganic copper salts in vitro, significantly increase the production of collagen by fibroblasts, except for a study conducted by Varghese et al 1986<sup>23</sup>, all the other studies showed an increased serum copper in patients with OSF and oral cancer when compared to normal controls. Trivedy et al, 1999<sup>24</sup> hold the view that, Copper released during chewing is brought in direct contact with the oral mucosa. Frequent chewing will raise the salivary copper level for a longer period allowing greater absorption through the mucosa. Copper is hypothesized to reach the connective tissue by transmucosal transport through the epithelial cells probably bounded to metallothionein protein, by non energy dependant diffusion (whereas in normal conditions, dietary copper when reaches the duodenum and jejunum, is absorbed as bound to albumin and transcuprin). In a study conducted by Master Luquman et al<sup>25</sup> brownish pigmentation was noticed in 40% of the cases. According to the study, the pigmentation could be due to an increase in the copper level which increases the tyrosine activity, leading to the increased pigmentations. It is seen that copper can upregulate the expression of the enzyme lysyl oxidase in the oral mucosa leading to fibrosis. One probable explanation is that the copper stabilizes the enzyme activity by increasing its half life. The second explanation is that, at the molecular level, the N-terminus of exon-1 of the lysyl oxidase molecule has copper binding sites and this interaction may upregulate the expression of the enzyme at the cellular level. These events lead to cross linking of collagen and elastin making it less degradable.

**Sequence of Events in Osmf:** It has been postulated that the earliest symptoms include burning sensation,

intolerance to spicy foods, blistering of the oral mucosa with ulcer and vesicles are common on the buccal mucosa, anterior faucial pillar, soft palate and labial mucosa. As the disease progresses, the mucous membrane develops a blanched appearance. Gradually the mucosa becomes thick and inelastic. Erythematous patches develop in the affected areas. Fibrosis of the mucosa occurs followed by stiffness most commonly in the palate, buccal mucosa, soft palate and then into the faucial pillars. As the disease further progresses, thick, inextensible fibrous bands develop vertically along the cheeks. Floor of the mouth becomes pale and thickened. In advanced cases, jaws are inseparable and the inelastic mucosa is forced against the buccal cusps of the teeth, where restorations or the sharp edges of the cusps cause ulcerations, which becomes secondarily infected. As the fibrosis involves the anterior faucial pillars and soft palate, the uvula becomes small and distorted. On palpation of the lower lip, circular bands of fibrous tissue are felt over the entire rima oris. As the pterygomandibular raphe is fibrosed, the base of the tongue, which is attached to it is pulled back and the patient complains of inability to protrude the tongue. Further atrophy of the papillae, dysgeusia and xerostomia are seen<sup>26</sup>.

Degree of trismus depends on the degree of fibrosis and the area of mucosal involvement. Other features reported include referred pain in the ear, deafness, nasal twang in the voice reported a relative loss of auditory function due to stenosis of the opening of the Eustachian tube. **P. C. Gupta (1980)** found oesophageal abnormalities more frequently in patients who had consumed Pan masala, Gutka, betel nut, tobacco or a combination of some or all of these, with or without betel leaf, for > or = 5 years compared to those consuming them for a shorter period of time. Oral submucosal fibrosis is not a disease confined to the oral cavity; the oesophagus may also be involved in about two-thirds of the patients with OSMF.

#### Treatment Modalities:

The treatment of OSMF has been palliative. Reduction or even elimination of the habit of arecanut chewing is an important preventive measure. The following treatment regimes for OSMF have been proposed.

1. Patient education (cessation of habit)
2. Physiotherapy
3. Medical line of 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 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. 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:** Patients with advanced oral submucous fibrosis given pentoxifylline at 400 mg 3 times daily showed Statistical improvement in all measures of objective (mouth 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

#### Surgical line of treatment

Surgical treatment is indicated in patients with severe trismus 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 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 anesthesia, may be a useful adjunct in managing oral submucous fibrosis.

### References:

1. S.C. Cox, D.M. Walker. Oral Submucous Fibrosis. A review; Australian Dental Journal 1996;41:5)
2. Bhonsle RB. et al. Tobacco habits in India. In: Proceedings of an international symposium, 15-19 January 1990. Bombay oxford university press, 1992 :25-46)
3. Mehta FS et al. An epidemiologic study of oral cancer and precancerous conditions among 101, 761 villagers in Maharashtra, India. Int. J Cancer 1972; 10:134-41
4. Su I Pin. Idiopathic Scleroderma of the mouth, Arch Otolaryngol 1954: 59: 330-2).
5. Shear et al. Oral Submucous Fibrosis in South African Indians: An Epidemiological Study; S Afr J Med Sci 1967; 32: 41-6, Shiau Y, Kwan H, Submucous Fibrosis in Taiwan, Oral Surg, 1979: 47: 453-7,
6. Pindborg JJ, Sirsat SM, Oral Submucous Fibrosis, 1966: 22: 764.
7. Sinor PN, Gupta PC, Mehta FS and Pindborg JJ. A case control study of oral submucous fibrosis with special reference to the etiological role of arecanut. Journal of Oral pathology and Medicine 1990; 19: 94-98.
8. Gunaseelan Rajan, Arecanut use in Rural Tamilnadu: A Growing Threat, Ind J Med Sci Vol 61, No.6 Jun 2007: 332 -337.
9. Arjungi KN, Areca nut: a review. Arsneimittelforschung 1976;26:951-956.
10. Glenn Morawetz, Oral submucous fibrosis, Int. J Oral Maxillofac. Surg. 1987: 16:609-614.
11. Hayes PA .Oral Submucous Fibrosis in a 4- year old girl. Oral Surgery 1985 ;59:475-478.
12. Abrol BM. Clinicopathological, biochemical and Immunological Studies in Syndrome of Idiopathic Oral Fibrosis. Bombay Hosp J 1977: 19:50-61.
13. Harvey W et al. Stimulation of human buccal mucosa fibroblasts in vitro by betal-nut alkaloids. Arch Oral Biol 1986;31: 45-49.
14. Hayes PA .Oral Submucous Fibrosis in a 4- year old girl . Oral Surgery 1985 ;59:475-478.
15. Scutt A et al. Stabilisation of collagen by betal nut polyphenols as a mechanism in oral submucous fibrosis. Experientia 1987; 3: 391-393.
16. Shah N, Sharma PP. Role of chewing and smoking habits in the etiology of Oral Submucous Fibrosis: a case control study. J Oral Pathol Med, 1998; 27: 475-479.
17. Rajendran et al. (2003) (Rajendran R J Oral and Maxillofac Path, Jan-Jun 2003 Vol 7, No 1, 145-149.
18. Maher R, Lee AJ, Warnakulasuriya KA, Lewis JA, Johnson NW. Role of areca nut in the causation of oral submucous fibrosis: A case-control study in Pakistan. J Oral Pathol Med 1994;23:65-9.
19. Trivedy and Warnakulasuryab, 2002). (Trivedy C, Craig G, Warnakulasuriya S. The oral health consequences of chewing areca nut. Addict Biology 2002;7:115-25.
20. Vander Bijl, 2001) Vander Bijl, Van Eyk AD, Van Wyk CW, Stander IA. Diffusion of reduced arecoline and arecaidine through human vaginal and buccal mucosa. Journa of Oral Pathology and Medicine 2001; 30: 200 – 205.
21. Nagabhushan, M., Amonkar, A.J., D'Souza, A.V. & Bhide, S.V. (1987) Nonmutagenicity of betel leaf and its antimutagenic action against environmental mutagens. *Neoplasma*, 34, 159–167.
22. Nair, U.J. et al (1990) Effect of slaked lime composition on the formation of reactive oxygen species from areca nut extract *in vitro*. *Carcinogenesis*, 11, 2145–2148.
23. Verghese Iype et al. Prevalence of oral submucous fibrosis among the cashew workers of Kerala – South India. Indian Journal of Cancer, 1986; 23: 101-104.
24. Trivedi C et al. The upregulation of lysyloxidase in oral submucous fibrosis and squamous cell carcinoma. J Oral Pathol Med 1999; 28: 246-251.
25. Master Luquman et al. The role of serum copper and iron in Oral Submucous Fibrosis, JIAOMR ;2004:16;01, 30-32.
26. Cannif JP, Harvey. OSMF – Pathogenesis and Management. British Dental Journal 1986; 160: 429-434.

### Corresponding Author

Dr.R.Christeffi Mabel M.D.S.,  
Af-3, Al-syed builders,  
2<sup>nd</sup> Main road, Dhandeeswaram Nagar,  
Chennai-600042  
Email: [christeffimabel@yahoo.co.in](mailto:christeffimabel@yahoo.co.in)