REVIEW OF ORAL SUBMUCOUS FIBROSIS: NEW CONCEPTUALIZATIONSINCLUDING ETIOPATHOGENESIS AND AYURVEDIC THERAPIES

Dr.Raghupathy.L.P[1*], Dr.Anuradha .G[2], Dr.Mathan Mohan.A[3], Dr.Thalaimalai Saravanan[4], Dr.K.R.Shakila[5], Dr.Aravindh Swamy.R.M[6],

Abstract:
Inflammation and increasing fibrosis in the submucous region are the hallmarks of oral submucous fibrosis, a precancerous condition that reduces tongue protrusion, an intense burning sensation, and trismus before making it difficult to open the mouth. Squamous cell cancer and hearing loss may develop as a result of negligence and untreated OSMF in advanced stages. Oral health issues are brought on by some bad human behaviours, such as chewing tobacco, pan masala, and areca nuts. Of them, oral submucous fibrosis (OSMF), oral mucous lesion (OML), leucoplakia, and erythroplakia are the most prevalent. OSMF is now recognisedon a global scale as being an Indian disease with the greatest prevalence of oral cancer. Numerous classifications based on histology, clinical grades, stages, types of cases, functional stages, etc. have been described in the medical literature over the years. Every classification offers benefits and drawbacks on its own. This study demonstrates current understanding of allreported classes, making it valuable for early diagnosis and treatment in academic and research settings. Etiopathogenesis factors have also been successfully covered in-depth in this case. This study aims to impart knowledge on the comprehensive use of ayurvedic medicines for OSMF. Here, we spoke about how ayurveda medicine is a far superior option than all other types of surgical and nonsurgical treatments. It is easier to treat the condition when habits are stopped and ayurvedic medicines are used properly in the early stages of OSMF.

Keywords: Oral submucous fibrosis **(**OSMF), Oral mucous lesion (OML), TMF, Areca nut, Collagen, Burning sensation, Blanching, Fibrosis, Carcinoma, Ayurvedic medicines.

[1*]Assistant Professor, Karpaga Vinayaga Institute Of Dental Sciences, Chinnakolambakkam.
[2]Professor and HOD ,SRM Dental college ,Ramapuram, Chennai.
[3]Professor and Dean ,Karpaga Vinayaga Institute Of Dental Sciences, Chinnakolambakkam.
[4]Professor and Vice Principal , Karpaga Vinayaga Institute Of Dental Sciences, Chinnakolambakkam.
[5]Professor, Karpaga Vinayaga Institute Of Dental Sciences, Chinnakolambakkam.
[6]Assistant Professor, Karpaga Vinayaga Institute Of Dental Sciences, Chinnakolambakkam.

***Corresponding Author:** Dr.Raghupathy.L.P
*Assistant Professor, Karpaga Vinayaga Institute Of Dental Sciences, Chinnakolambakkam.

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INRODUCTION

A premalignant condition called oral submucous fibrosis (OSF) is connected to chewing areca nuts (betel nut). The practise is common among South Asian cultures, but it is now alsoacknowledged in North America and Europe. Significant morbidity is a result of OSF. It also causes death after developing into squamous cell carcinoma (SCC). The frequency of OSF has significantly increased as a result of the areca nut and tobacco combo.

SYNONYMS:

- Submucous fibrosis of the palate and pillars (Joshi, 1952).
- Diffuse oral submucous fibrosis (Lal 1953).
- Idiopathic scleroderma of mouth (Su, 1954).
- Submucous fibrosis of the palate (Sirsat and Khanolkar, 1957, 1960, 1962).
- Submucous fibrosis of palate and cheek (Desa, 1957).
- Idiopathic palatal fibrosis (Rao, 1962). Juxta epithelial fibrosis(Pindborg 1964)
- Oral submucous fibrosis (Pindborg and Sirsat, 1966).
- Subepithelial fibrosis (Goleria, 1970).
- Idiopathic oral fibrosis (Krishnamoorthy, 1970).

DEFINITION

The most widely accepted definition is by Pindborg JJ and Sirsat SM (1966). They havedefined OSMF as an insidious chronic disease of unknown etiology affecting the mucosa of any part of oral cavity and occasionally extending to pharynx and oesophagus and rarely to larynx. The condition "sometimes preceded by and associated with juxta-epithelialinflammatory reaction followed by a fibro-elastic change of the lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and inability to eat.

ETIOLOGY

Stimuli cause an inflammatory response in the juxtaepithelium of the oral mucosa, which startsthe illness process. OSMF is thought to have a complex aetiology. Numerous factors have been proposed as contributing causes, including betel nuts, cigarettes, smoking, pan masala, chillies, starvation, vitamin deficiencies, autoimmune disease, and genetic susceptibility. One of the most significant risk factors for OSF has been identified as chewing betel quid (BQ), which may contain tobacco, areca nuts, slaked lime, or other species.

BETEL QUID

to definitions, "quid" is "a substance, or mixture of substances, inserted in the mouth or chewed and remains in contact with the mucosa, usually comprising one or both of the two primary ingredients, tobacco and/or areca nut, in raw or any manufactured or processed form." BQ typically comprises of areca nut (betel nut), slaked lime, catechu, and various seasonings to taste, all wrapped in a betel leaf. The endosperm of an Areca catechu fruit is known as an areca nut.

There are many techniques to process betel nuts, including boiling, roasting, and soaking. Nut roasting has virtually little impact. Nuts' tannin content is significantly reduced and their detectable alkaloids are eliminated when they are soaked and then cooked in water.

These are all some of the commercially available areca nut mixtures

Name of Mixtures	Components
Betel Quid	Areca Nut, Tobacco, Fresh Betel Leaf, Slaked Lime and Catechu
Pan Masala	Areca Nut, Slaked Lime, Catechu and Condiments.
Gutka (Gutkha)	Pan Masala and Tobacco
Mainpuri	Areca Nut, Tobacco, Slaked Lime, Camphor and Cloves
Mawa	Areca Nut, Tobacco and Slaked Lime
Khaini	Tobacco, Slaked Lime

Chewing betel is done for a variety of reasons, including exhilaration, increased salivation, hunger satisfaction, tooth pain relief, etc. Individual chewing habits vary, but typically the BQ is placed in the buccal vestibule for 15 to 60 minutes, five to six times a day.

Arecoline, arecaidine, arecolidine, guyacoline, and guacine are the main areca nut alkaloids. Tannins and catechins are the key flavonoid components of areca nut. Alkaloid arecoline is the most prevalent. The notarization of these alkaloids results in N-nitrosamines, which may be harmful to cells. It has been shown that arecoline encourages the synthesis of collagen.

The combination is constantly in contact with the oral mucosa. The BQ's alkaloids andflavonoids are ingested and go through metabolism. Oral tissues are constantly irritated by these components and

their metabolites. The coarse fibres of the areca nut irritate the oral mucosa mechanically in addition to chemically from the BQ components and their metabolites. Additionally, juxta-epithelial inflammatory cell infiltration is caused by the transport of BQ alkaloids and flavonoids into the Subepithelial connective tissue, which is facilitated by the friction of the areca nut's coarse fibres.

Any external force that injures tissue in any way can trigger a defensive inflammatory response. Chronic inflammation develops at the place over time as a result of continuous habit. The mucosa becomes more atrophy and ulcerated as a result of the initial irritation.

TOBACCO:
It may act as a local irritant in oral submucous fibrosis

LIME:
It causes local irritation. Betalnut and lime are chewed together. It damages the mucosa locally, causing vesicle and ulcer development as well as localised irritation.

Prolonged Local Irritation:

Chili:
Dietary factors are thought to be connected to the etiology of OSMF because it is localised in the upper digestive system. Indians who reside in southern states consumes chili at every meal, either raw or as dried powder. It has been established that "capsaicin," an active extract from chilies (capsicum annum and capsicum frutescence), acts as an irritant. It alters connective tissues and causes oral mucosa injury.

BACTERIAL INFECTION:
Streptococcal toxicity is also factor in etiology of Oral Submucous Fibrosis.

IMMUNOLOGICAL DISORDER:
In some circumstances, circulating autoantibodies are present. Immunoglobulin A, M, and Gare also suggestive of immunological disease in addition to this elevated ESR.

GENETIC COMPONANT:
Given that there have been reported cases of OSMF without a history of betel nut chewing, a genetic component is thought to be implicated.

Patient with OSMF have increases frequency of HLA-A10, .HLA-B7, HLA-DR3.

HEREDITARY PREDISPOSITION:
OSMF is more prevalent in India and among Indians who live abroad. These people may be genetically predisposed to submucosal fibrosis, making their oral mucosa vulnerable to chronic inflammatory alterations brought on by exogenous agents including areca, alkaloids,and tannins.

The disease primarily affects South East Asia and India, but cases have also been observed inKenya, China, the UK, Saudi Arabia, and other regions of the world where Asian immigrants are migrating. (13) According to a research from Jodhpur, India, 64% of patients had one or more lesions, with OSMF accounting for 30% of those diagnoses. (14)
The key reason why the OSMF male to female ratio was 2.7:1 in another study from Patna and other areas of Bihar is the use of strong spices, chillies, and gutkha. (15) Similar findings from another study indicated that the prevalence of chewing Gutkha and Pan masala was 6.3% in Moradabad patients. (16)

The prevalence of oral mucosal lesions (OML) was 16.8% overall in Uttar Pradesh, with smokers' palate accounting for the majority of cases (10.44%), followed by leukoplakia (2.83%), OSMF (1.97%), oral lichen planus (0.8%), and other conditions all brought on by the habit of chewing tobacco and its various products. (17)

A house-to-house study conducted in the Maharashtra area of Pune revealed that 0.03% of OSMF patients have been diagnosed. The same survey was also conducted in Bhavnagar, Gujarat, with 5018 men, and 164 of them had OSMF, with a 3.2% occurrence rate. (18)

Another study was carried out in the semi-urban Sangli district of Western Maharashtra, where 152 of the 623 patients had OSMF. (19) The frequency of OSMF was 2.01% in Kerala, a region in Southern India, and 4.1% of the population had oral mucosal lesions (OML). With a male tofemale ratio of 99:1, chewing tobacco and areca nuts was reported to be 8% prevalent in Chennai. (20).

Because tobacco and areca nut products are sold in a variety of appealing pouches, OSMF is more prevalent in younger generations. (21) According to a study by Sirsal and Khanolkar, themajority of OSMF cases are among people between the ages of 20 and 40. (22) Sinol el at stated that 25–34 year old age groups accounted for the majority of OSMF cases, with 79% ofpatients being under the

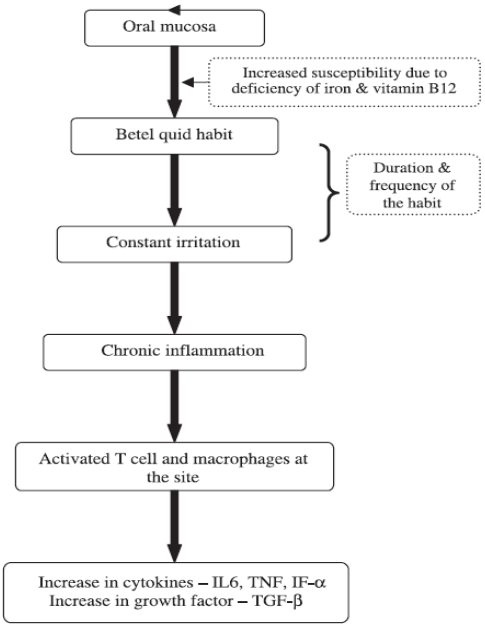
age of 35.

Hazarey et al. identified OSMF patients in a different study from Nagpur, Maharashtra, who were under 30 years old and had a male to female ratio of 5:1. (23)

PATHOGENESIS

The oral submucosal collagen deposition is a significant histologic feature of OSF. By generating an aberrant rise in collagen formation, the areca nut (betel nut) component of BQ, particularly an alkaloid called arecoline, plays a significant role in the pathophysiology of OSF.

OSF may be regarded as a collagen-metabolic condition brought on by areca nut intake. The connective tissues' fundamental structural component, collagen, must be maintained in each tissue's composition to ensure adequate tissue integrity. Growth factors, hormones, cytokines, and lymphokines are only a few of the mediators that have an impact on collagen synthesis. Transforming growth factor-beta (TGF-b) is a well-known mediator; TGF-b1 in particular appears to be crucial for wound healing and fibrosis.

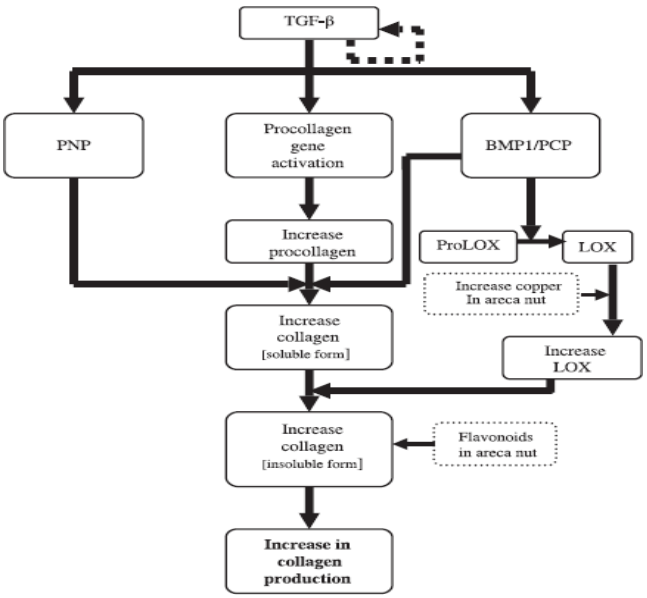


The oral mucosa, which has ongoing irritation due to habitual indirect contact with BQ, is the site of the disease's initial episodes. As a result, inflammatory cells including T cells and macrophages are present in a chronic inflammatory condition. Different cytokines and growth factors are released by these cells, and/or they are stimulated to produce., Interleukin 6 (IL6), tumour necrosis factor (TNF), interferon alpha (IF-a), and transforming growth factor-beta (TGF-b)

The presence of activated T lymphocytes, macrophages, etc. is a sign of inflammation. Different chemical mediators of inflammation are elaborated, with prostaglandins (PGs) playing a crucial role. It has been demonstrated that oral keratinocytes produce PGs in response to areca nut extract (ANE). The development of cancer and tissue fibrosis depends on aberrant and persistent tissue inflammation.

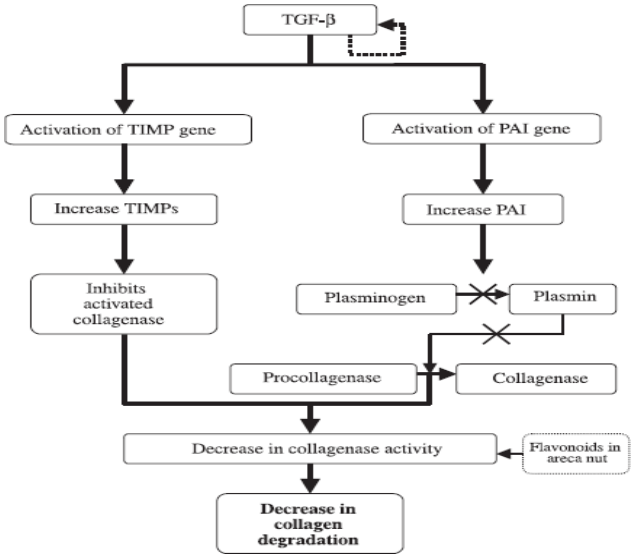
Therefore, it can be said that the BQ components' production of oral mucosal inflammation is a crucial step in the aetiology of OSF. At the location of inflammation, cytokines like interleukin 6, tumour necrosis factor (TNF), interferon, etc., and growth factors like TGF-b are produced. It has been proven that people who are anaemic from iron or vitamin B12 deficiency are more vulnerable.

This can be because there is more BQ absorption due to the mucosa's higher fragility. A crucial regulator of ECM synthesis and remodelling is TGF-b1. TGF-b primarily affects the genes involved in the production and breakdown of the ECM at the transcriptional level via nebulous intracellular mechanisms. The pathways for collagen formation and breakdown, which are controlled by TGF-b and the flavonoids in areca nut, are covered in two main sections of this review.



TGF-b regulation of the collagen synthesis pathway: A growth factor with autocrine action is TGF-b. More pro-collagen is produced as a result of the procollagen genes being activated. Additionally, it stimulates the release of PCP and PNP, two substances necessary for the transformation of pro-collagen into collagen fibrils.

Increased collagen cross-linking in OSF leads to an increase in insoluble form. An important enzyme called LOX, whose synthesis and activity have risen, makes this easier. A crucial component in the pathophysiology of this disease, LOX activity is stimulated by PCP/BMP1 and elevated copper (Cu) in BQ. The collagen fibers' cross-linking is accelerated by flavonoids. Increased collagen production is the result of these actions. Pro-LOX stands for pro-lysyl oxidase, LOX for lysyl oxidase, BMP1 for bone morphogenetic protein 1, PNP for pro-collagen N-proteinase, and PCP for pro-collagen C-proteinase.



TGF-b controls the collagen breakdown pathway by activating the genes for TIMPs, which leads to the formation of additional TIMP. The enzyme collagenase, which is required for the breakdown of collagen, is inhibited by this. There is no plasmin production since it also activates the gene for PAI, an inhibitor of plasminogen activator. Pro collagenase must be converted into an active form by plasmin, and plasmin deficiency leads in the absence of active collagenase. The collagenase activity is inhibited by flavonoids. Collagen breakdown decreases as collagenase activity and concentrations are reduced. Transforming growth factor-beta, plasminogen activator inhibitor, and tissue inhibitor of matrix metalloproteinase are all abbreviations for the same compound.

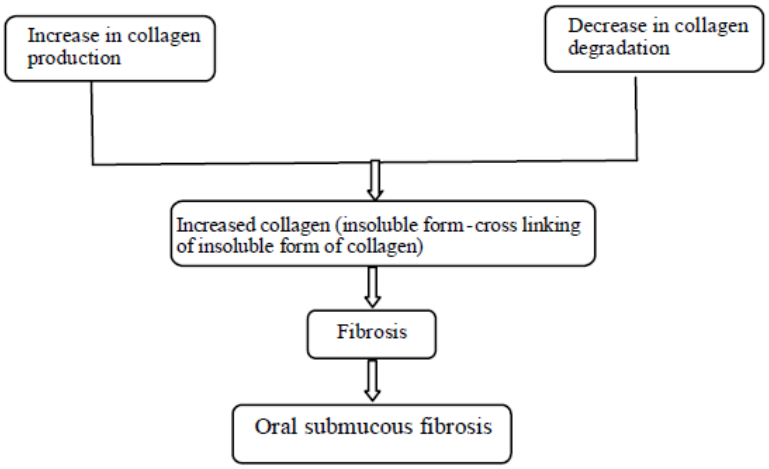


Figure 2: Overall effect of activated TGF beta pathway. There is in increase n collagen production and cross linking (insoluble form) along with the decrease in the collagen degradation. This produces increased collagen deposition in the subepithelial connective tissue layer of the oral mucosa leading to OSF

CLINICAL FEATURES

The symptoms of OSMF are:

1) Burning sensation and blanching of oral mucosa.
2) Moderate limit of mouth opening.
3) Bud shaped or shrunken ovula.
4) Depapilated tongue and ulceration on tongue.
5) Blister or marble like appearance on soft palate and inflammation in oral mucosa occurs.
6) Mobility of tongue and soft palate decreases.
7) Excessive salivation and bad breathe.

CLINICAL GRADING:

I.Pindborg and Sirsat(1966) clinically graded OSMF as

VERY EARLY: Severe marked fibrosis of cheek, palate, lips, uvula, tongue and narrow opening of the mouth.

EARLY: Along with the above symptoms there is slight difficulty in opening the mouth.

MODERATE: There is marked trismus, where patient cannot open his mouth more than 2 fingers. There is difficulty in mastication.

ADVANCED : Patient is under nourished, anaemic with marked degree of trismus and other associated symptoms of OSMF.

II. Ahuja SS and Agarwal GD (1971) in their article classified submucous fibrosis clinically depending on the extent and type of fibrosis[71].

Class-I: Localized fibrous bands in the cheek extending from the superior to inferior vestibular fornix on one or both sides. In the order of frequency, the bands are usually located on the lipsin the premolar region and 2nd molar region.

Class-II: Generalized diffuse hardening of the subepithelial tissues. Thus hardening usually extends from the cheek and hard palate to the soft palate, uvula and the pillars of the fauces. In occasional cases, the hardening might extend to the lining mucous membrane of the pharynx.

Class-III: Combination of above 2 types where the fibrous bands are associated with a generalized diffuse form of submucous fibrosis.

III. Bhatt AP and Dholakia HM (1971)[72] in their study, they clinically grouped the patients into three grades:

Grade-I: Comprised of mild and early cases with a very slight fibrous bands and little closer of mouth.

Grade-II: Moderately pronounced symptoms of the disease with fibrous banding extending from cheek to palate area.

Grade-III: Markedly excessive amount of fibrous banding involving cheek, palate, uvula, tongue and lips and restricting the opening of mouth.

IV. Gupta DS et al (1980) clinically classified 4 stages of submucous fibrosis as per the increasing intensity of trismus[73].

1. Very early stage: The patients complained of burning sensation in the mouth or ulceration without difficulty in opening the mouth.
2. Early stage: Along with the symptoms of burning sensations, patients complained of slight difficulty in opening the mouth.
3. Moderately advanced stages: The trismus is marked to such an extent that patient cannot open his mouth more than 2 fingers. Patient

therefore, experience difficultyin mastication.
4. Advanced stage: Patient is undernourished, anemic and has a marked degree of trismus and/ or other symptoms as mentioned above.

V. Mathur RM and Jha T (1993) done the following staging of OSMF[74].

Stage-1: Early OSMF:
a) Mild blanching
b) Mouth opening normal.
c) No restriction in tongue protrusion.
d) Burning sensation – only on taking spicy food or hot temperature liquids, etc.

Stage-2: Moderate OSMF:
a) Moderate to severe blanching.
b) Mouth opening reduced by 33%, tongue protrusion reduced by 33%, flexibility also demonstrably decreased.
c) Burning sensation even in the absence of stimuli.
d) Palpable bands felt.
e) Lymphadenopathy either unilateral or bilateral.
f) Demonstrable anemia on hematological examination.

Stage-3: Severe OSMF:
a) Burning sensation very severe, patient unable to do day-today work.
b) More than 66% reduction in the mouth opening, cheek flexibility and tongue protrusion. In many, the tongue may appear fixed.
c) Ulcerative lesions may appear in cheek.
d) Thick palpable bands.
e) Lymphadenopathy bilaterally present.

VI. Naidu SM et al (2000) studied 325 patients suffering from oral submucous fibrosis. Their purpose of study was to stage the severity of the disease with (functional staging) using an objective measure (inter-incisional opening) and to study its relationship to clinical staging. They staged the disease clinically and functionally.

Clinical Staging:
Stage-I:
Faucial bands only.

Stage-II:
Faucial and buccal bands

Stage-III:
Faucial and labial bands.

Functional Stage:
Stage-A:
Mouth opening 13-20 mm

Stage-B:
Mouth opening 11-10 mm

Stage-C:
Mouth opening < 10 mm.

VII. Kacker SK states that patients can be grouped into 3 stages.

Stage-I: Stage of Stomatitis and Vesiculation:
- Characterized by recurrent stomatitis and vesiculation. Patient complains of burning sensation in the mouth and inability to eat pungent food.
- The examination reveals vesicle on the palate. They may rupture and a superficial ulceration may be seen. Some amount of fibrosis can be seen.

Stage-II: Stage of Fibrosis:
There is inability to open the mouth completely and stiffness in mastication. As disease advances there is difficulty in blowing out cheek and difficulty in protruding the tongue. On examination, there is increasing fibrosis in the submucosa. Mucosa is blanched and white, lipsand cheeks are stiff. The salivary glands are normal. Dorsum of tongue may show atrophy of papillae. Blanching and stiffness of the mucosa of the floor of the mouth is less marked than that seen in the lips, cheek and palate. Larynx is free from disease and respiration is not affected.

Stage-III: Stage of sequelae and complications:
Leukoplakic changes in the mucosa. An ulcerating malignant lesion may be seen involving the cheek, oropharynx, tongue. There is evidence to suggest that OSMF is a precancerous condition. The mechanism involved in the development of oral cancer in patients with OSMF is not yet understood. It is generally accepted that atrophic epithelium is more likely to undergo malignant changes than epithelium of normal thickness. Thus, the patient with OSMF may be predisposed to develop oral cancer under the influence of carcinogens.

Classification of oral submucous fibrosis: Passi D *et al*. (2017)

Grading/ staging	Clinical	Functional	Histopathological	Treatment	Prognosis
Grade 1	Involvement of less than one-third of the oral cavity Mild blanching, burning sensation, recurrent ulceration, and stomatitis. dryness of mouth	Mouth opening up to 35 mm	Stage of inflammation: Fine edematous collagen, congested blood vessels, abundant neutrophils along with lymphocytes with myxomatous changes in subepithelial, connective tissue layer of epithelium	Cessation of habit, nutritional supplement, antioxidants, topical steroid ointment	Excellent
Grade 2	Involvement of one-third to two-third of the oral cavity Blanching of oral mucosa with mottled and marble like appearance, fibrotic bands palpable and involvement of soft palate and premolar area	Mouth opening 25-35 mm Cheek flexibility reduced by 33%	Stage of hyalinization: Juxta-epithelial collagen hyalinization with lymphocytes, eosinophils. Dilated and congested blood vessels. Less fibroblastic activity. Granulation changes in muscle layer with reduced inflammatory cells in subepithelial layer	Habit cessation, nutritional supplement, intralesional injection of placental extracts, hyaluronidase, steroid therapy Physiotherapy	Good Recurrence rate is low
Grade 3	Involvement of greater than two-third of the oral cavity. Severe blanching, Broad thick fibrous palpable bands at cheeks and lips and rigid mucosa, depapillated tongue and restricted tongue movement and shrunken bud like uvula. Floor of the mouth involvement and lymphadenopathy	Mouth opening 15-25 mm Cheek flexibility reduced by 66%	Stage of fibrosis: Complete collagen hyalinization without fibroblast and edema. Obliterated blood vessels Plasma cells and lymphocytes are present Extensive fibrosis with hyalinization from subepithelial to superficial muscle layers with atrophic, degenerative changes	Surgical treatment including band excision and reconstruction with BFP or split thickness graft bilateral temporalis myotomy and coronoidectomy	Fair Recurrence rate is high
Grade 4	Leukoplakia changes, erythroplakia Ulcerating and suspicious malignant lesion	Mouth opening <15 mm or nil	Stages of malignant transformation: Erythroplakia changes into squamous cell carcinoma	Surgical treatment and biopsy of suspicious lesion	Poor, malignant transformation

Classification based on all parameters like clinical features, histopathology and managements was developed by Khanna JN and Andrade NN as follows: (52)

Group I:

Very early cases: Common symptoms as: burning sensation, ulceration. No restriction in mouth opening.

Histology: Fine fibrillar collagen, inflammatory cell exists, normal epithelium.

Group II:

Early cases: Marble like appearance on palate, fibrosis palpable. Interincisal distance of 26 to 35mm.

Histology: Blood vessel congested, depapilated tongue, progressive fibrosis, increase in inflammatory cells mainly consists of lymphocytes and few eosinophils observed.

Group III:

Moderately advanced cases: Trismus occurs, vertical fibrous bands formed on soft palate, anterior faucial lesion on oral mucus. Atrophy of underlined mucosa, thick collagen fiber band and thickened muscle fibre observed.

Histology: Hyalinised Juxta- epithelium, dense collagen bundle, residual edema, congested blood vessels, and mature fibroblast with spindle-shaped nuclei, marked epithelium, inflammatory cells like lymphocytes, eosinophils, neutrophils and plasma cells increases inlarge amount in oral mucosa.

Group IV (A):

Advanced cases: Severe trismus, bud shape or shrunken ovula, thickened faucial pillars,restricted tongue movement and mouth opening. Interincisal distance is less than 15mm.Group IV (B):

Group IV (B):

Advanced cases: Squamous cell carcinoma, hyper keratotic leukoplakia.

Histology: Hyalinised collagen, extensive fibrosis, complete loss of epithelial cell, extensive muscle degeneration. Oral cancer occurs.

HISTOLOGICAL FEATURES INITIAL STAGE

Juxta-epithelial inflammation including edema, large fibroblasts and an inflammatory infiltrate, consisting primarily of neutrophils and eosinophils.

Later, collagen bundles with early hyalinization are seen and the acute inflammatory infiltrate contains more chronic cell types, such as lymphocytes and plasma cells, occasionally resembling lichenoid mucositis.

ADVANCED STAGES

OSF is characterized by formation of thick bands of collagen and hyalinization extending into the submucosal tissues and decreased vascularity. The epithelium lining frequently becomes thin and loses melanin.

HISTOLOGICAL GRADING:

I. Pindborg and Sirsat histologically graded OSMF as

VERY EARLY:

Finely fibrillar collagen dispersed with marked edema.

EARLY:
Juxta epithelial area shows early hyalinisation, the collagen is thick and seen in separate bundles, less number of fibroblast, blood vessels are dilated and congested, inflammatory cellsare seen.

MODERATE:
The collagen is moderately hyalinized, thickened collagen bundles, a smaller number of fibroblasts, fibrosed blood vessels, inflammatory cells are seen.

ADVANCED:
The collagens are completely hyalinized and is seen as smooth sheath, with no separate bundles. Edema is absent. Hyalinized areas are devoid of fibroblast. Blood vessels are completely obliterated, narrowed. Few inflammatory cells are seen.

FUNCTIONAL GRADING

I.**Haider(2000**) functionally graded OSMF as
STAGE A: Maximal mouth opening>20mm
STAGE B: Maximal mouth opening=10-19mm
STAGE C: Maximal mouth opening<10mm
II. To aid in treatment planning**, Khanna and Andrade** developed a classification system of OSF based on interincisal opening (MIO), as follows.

Group 1.
Early OSF without trismus (MIO >35 mm).

Group 2.
Mild to moderate disease (MIO 26–35 mm).

Group 3.
Moderate to severe disease (MIO 15–26 mm).

Group 4a.
Severe disease (MIO <15).

Group 4b.
Extremely severe; malignant or premalignant lesionsnoted intra-orally.

Pindborg JJ (1972) summarized a criteria to support the precancerous nature of this disease as:

1. Higher prevalence of leukoplakia among submucous fibrosis patients.
2. Higher frequency of epithelial dysplasia.
3. Concurrent findings of submucous fibrosis in oral cancer patients
4. Histological diagnosis of oral cancer without clinical suspicion among submucous fibrosis cases.
5. Higher incidence of oral cancer among patients with submucous fibrosis

AYURVEDIC TREATMENTS:
For OSMF, a number of surgical and nonsurgical therapies are available. Ayurvedic therapyis one of them. (53)

Definition:
Ayu means life and veda means wisdom in Sanskrit. Ayurveda is the name of the living science that incorporates a comprehensive approach to healthcare. It is one of the world's oldest medical systems (54). Incurable diseases including cancer, diabetes, asthma, arthritis, etc. can also be treated with it.
According to the World Health Organization, between 70 and 80 percent of people worldwide rely on ayurvedic medicine (WHO). (55) Ayurvedic medicine has been practised in India since ancient times, according to the shastra. Due to its efficacy, efficiency, and effectiveness in curing the incurable condition, it has gained more notoriety in recent years. Dental issues including periodontitis, oral lichen planus (OLP), tooth issues, oral cancer, OSMF, oral mucus lesions (OML), etc. may all be treated easily with ayurvedic remedies. There are numerous research that demonstrate how ayurvedic treatments or medicines can be used to treat OSMF. (56)

i. Turmeric:
Curcuma longa, another name for turmeric, is a member of the ginger family. Turmeric's primary chemical component is curcumin. Its non-toxic properties include anti-inflammatory, antioxidant, antibacterial, analgesic, hepatoprotective, antimutagenic, antiseptic, expectorant, antifungal, antiviral, and antiplatelet agents. It also functions as an expectorant. Since ancient times, curcumin, a naturally occurring yellow pigment in plant rhizomes, has been widely utilised in ayurvedic treatment. (57)
A 2010 study by Balwant Rai et al. to understand the mechanism of action for curcumin in patients with preadvanced stage OSMF. By boosting the levels of vitamin C and vitamin E, itdemonstrated the reduction of malignant cells. It also shown the prevention of DNA damage by acting as pro-oxidant and anti-oxidant qualities. Agarwal N. et al. conducted a second trialin 2014 to examine the effectiveness of turmeric in thirty OSMF patients. It has been observed that turmeric suppresses inflammatory cells and speeds up collagen degradation. In a similar vein, a 2015 study by Deepa Rao et al. examined the effectiveness of turmeric (Curcumin) in two forms, namely capsule and oil, in 48 OSMF patients. Patients

who received it experienced anti-inflammatory and fibrinolytic effects. (58–60)

ii. Tulsi:

Ocimum sanctum linn is another name for tulsi. It has ursolic acid (UA), which boosts resistance. Olenoic acid, rosemarinic acid, eugenol, carvacrol, - carypphyllene (8%), -eleme (11.0%), and germacrene D (2%), among others, are also present. By blocking enzymes, it has anti-inflammatory, analgesic, antioxidant, anti-stress, anti-septic, and other effects. (61)

According to a 2017 study by G. Madhulata et al, Tulsi is a miracle herb for treating OSMF. "Tulsi as a queen of herbs," they said. The outcome was an increase in patients' mouth opening distance. (62)

iii. Aloe-Vera:

Aloe-Vera is a member of the Asphodiaceae family and has two distinct species: Aloe barbedensis and Aloe abrorescens. It is a green plant that resembles a cactus; its mucilaginous gel is made up of 98–99% water and 1%–2% active ingredients. Humans have been using aloe since the sixteenth century BC.

Aloe Vera is referred to as "the plant of immortality" in a study. Lupeol, salicylic acid, isorabiachromone, feruoylaloesin, p-coumarylaloesin, and other chemicals make up the majority of it. Aloe Vera is utilised in medicine as an immunological stimulator, analgesic, anti-inflammatory, and more. (63)

Dose: Aloe-Verajuice- drink twice a day for 3 months; gel on scoop- applied 3-4 times aday for 3 months. (64)

Study published in May 2012 by Sudarshan et al. showed that utilising aloe vera gel reduced burning sensation, enhanced mouth opening, and increased cheek flexibility in OSMF patients. (65)

Ardra Anuradha et al. conducted a study in 2016 that used aloe vera juice and gel in two distinct patient groups, A and B, respectively. The results satisfactorily demonstrated that the burning sensation had decreased in both groups and that the mouth opening distance had improved. However, group A's outcome was attained more quickly thangroup B's. (66)

iv. Immune Milk:

Immune milk is cow's milk that has been exposed to a variety of human intestinal microbes. It quickly boosts immunity and has a positive anti-inflammatory impact. Vitamins A, C, B1, B2, B6, B12, nicotinic acid, pantothenic acid, folic acid, iron, copper, and zinc are all present in immune milk. 20–30% of the antibodies are also present (IgG type I). (67)

In a 2011 research by Tai et al., OSMF patients received 45 grams of vaccinated milk powder twice day for three months. Improvement in patient symptoms was noted as a result.

v. Tomatoes:

Lycopene, an antioxidant produced by plants, is found in tomatoes. It works as an anti-cancer drug by preventing the synthesis of collagen. (68)

A 2011 study by B. Gowda et al. that looked at how lycopene affected OSMF patients. One set of patients received lycopene administration, and the other group received alternative treatment. According to the OSMF findings, lycopene patients had better interincisal and mouth opening improvements. (69)

J. Johny et al. presented a different study in 2019 that compared the effects of lycopene and lycopene-hyaluronidase in OSMF patients. They separated the patients into 2 groups: group A received lycopene, group B received lycopenehyaluronidase (group B). Compared to group A, group B's symptoms appeared to have improved more. (70)

vi. Spirulina:

A blue-green microalga called spirulina contains protein, carotene, and other elements. It has a high concentration of beta-carotene, which serves as an antioxidant and helps to decrease tumour necrosis factor (TNF) and inflammatory cells. (71)

vi. Others:

Withania somnifera (Ashwagandha), Glycyrrhiza glabra (Liquorice), Wheat (Tritium sativum), European grapes (Vitis vinifera), and Yashada bhasma are the main ingredients in the Oxitard formulation.

Dose: 2 capsules twice a day for 3 months.

Singh et alstudy .'s from 2014 showed that using the oxitard capsule for three months was effective for 48 OSMF patients. They came to the conclusion that patients' mouth openness had improved along with a decrease in pain and lesions. (72)

vii. Combination Therapy:

Combining ayurvedic medicines also yields improved outcomes for OSMF. There are many studies that combine the medicines and show superior outcomes.

Yadav M. et al. did a study in 2014 that compared the use of turmeric and steroid injection in OSMF patients. The outcome was a decrease in burning

sensation, a reduction in tongue protrusion, and an increase in interincisal distance. (73)

Aditi Shrivastava et al. published a study in 2015 that evaluated the synergistic effects of turmeric and tulsi in combination for OSMF patients. (74)

A study conducted in 2014 by Patil et al. compared the effectiveness of Oxitard and Aloeverain 60-60 people. Aloe-vera was found to have an added benefit in their study's combination therapy, which led to improvements in mouth opening and lesion healing. Similar studies have shown higher improvement in OSMF when oxitard, immune milk, and spirulina are combined with aloe vera. (75)

CONCLUSION:

Oral submucous fibrosis (OSMF) is a chronic, progressing condition that is precancerous. It is one of the diseases that is handled in an absurd and unacceptable way. Although its genesis is unknown, it has been determined from all published studies and literature that areca nut, tobacco, and pan masala are the disorders' causal agents.

The prevalence of OSMF is considerable in India as a result of the market's sale of commercial tobacco-containing products. The goal of this study is to comprehend current understanding of pathophysiology and etiology.

People must be made aware of the negative effects of areca nuts and other items. By putting "Intake of tobacco causes cancer" on packets, the Indian government has already begun the initiative to make people aware, however some individuals continue to use all these items as a result of their established habits.

Here, it has been successfully established that updated classifications including all clinical stages, histological findings, grading, and symptoms for early diagnosis can aid with early illness diagnosis and treatment. However, an alternative treatment using Ayurvedic medicines demonstrates efficacy and success in alleviating symptoms while other surgical and non- surgical treatments for OSMF are only partially beneficial.

Additionally, Ayurvedic medicine guarantees the absence of any drug-related negative effects. It is conceivable that ayurvedic treatment for OSMF produces superior outcomes to other surgical and nonsurgical procedures.

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