

REVIEW ARTICLE

RECENT CONCEPTS OF ETIOPATHOGENESIS AND MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A REVIEW OF LITERATURE

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ABSTRACT: Oral submucous fibrosis (OSF) is a well-recognized chronic insidious disease, precancerous condition, autoimmune and collagen related disorder which is multifactorial in origin mainly associated with the practice of chewing betel quid containing areca nut, a habit common among lower socio-economic strata of society. It is characterized by inflammation, increased deposition of submucosal collagen and formation of fibrotic bands in the oral and paraoral tissues, which increasingly limit mouth opening. In the myriad of literature available, numerous etiology and management techniques are put forward by various authors in the past. In this paper, an attempt is made to analyze critically and update the knowledge of the recent developments that enhances the understanding of the etiology of this premalignant condition and its medicinal & surgical management which improves the life expectancy.

KEYWORDS: Oral Submucous Fibrosis, Betel Nut, Collagen Bands, Treatment.

INTRODUCTION: Oral submucous fibrosis is a precancerous condition, first described by Schwartz in 1952 as atropica idiopathica (Tropica) mucosae oris.^[1,2] It is also known as idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, sclerosing stomatitis, diffuse oral submucous fibrosis and submucous fibrosis of the palate and pillars.^[3] It is a chronic, insidious disease affecting the oral cavity and sometimes pharynx. It originates with vesicle formation and is always associated with juxtaepithelial inflammatory reaction followed by fibro elastic changes in the lamina propria with epithelial atrophy.^[4] It is characterized by the progressive buildup of constricting bands of collagen in the cheeks and adjacent structures of the mouth, which can cause problems with speech and swallowing and severely restrict mouth opening and tongue movement leading to difficulty in eating.^[5,6] OSMF has been documented in the Indian population since the time of Sushruta- a renowned Indian physician (Circa sixth century BCE) as Vidari, the features of which simulate Oral Submucous Fibrosis, and is more often seen in South Asian countries.^[7,8] In recent years the prevalence rate reported in India is up to 6.42% with predominance in males of age 20-40 years.^[9]

In initial phase of disease, mucosa feels leathery with palpable fibrotic bands. In advanced stage the oral mucosa loses its resiliency and becomes blanched and stiff. Other features of disease include xerostomia, recurrent ulceration and pigmentation of oral mucosa, dryness of mouth, burning sensation, decreased mouth opening and tongue protrusion.^[10] Histopathological examination shows subepithelial fibrosis and chronic inflammation accompanied by hyalinization and loss of vascularity, squamous hyperplasia with parakeratosis.^[11] Its precancerous nature was first described by Paymaster in his study of 650 Indian patients and he found that one third of patients had onset of slowly growing squamous cell carcinoma.^[12] It causes significant morbidity (In terms of loss of mouth function) and mortality (When transformation into squamous cell carcinoma occurs).^[13] The term oral submucous fibrosis was finally given by Joshi in 1953.^[14]

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Incidence & Epidemiology: The condition is found in 4/1,000 adults in rural India and as many as 5 million young Indians are suffering from this precancerous condition. OSMF is predominantly seen in people in south Asian countries,^[15] such as India, Bangladesh, Bhutan, Pakistan and Sri Lanka, or in south Asian immigrants to other parts of the world.^[16,17] Cases have occasionally been reported in Europeans; it also occurs in people from Taiwan, China, Nepal, Thailand and Vietnam.^[18] The younger generation are suffering more due to incoming of areca nut products in different multicolored attractive pouches.^[19] Sporadic cases have been reported in other ethnic groups from countries such as Taiwan.^[20]

Sirsat and Khanolkar reported majority of OSMF cases belonged to the age group of 20-40 years of age.^[21] Sinor et al reported 79 per cent of the OSMF cases were under the age of 35 years and maximum numbers of cases were in 25-44 years of age group.^[22] Shah and Sharma in their study numbers of cases were in 25-44 years of age group.^[23] A case-control study of 185 subjects in Chennai, South India revealed a male-to-female ratio 9.9:1.^[24] In Patna, Bihar (Also in India), the male-to-female ratio was 2.7:1.^[19] Hazarey et al from Nagpur also reported that most of their patients were in the younger age group (< 30 years) with a similar male to female ratio of 5:1.^[25]

Etiopathogenesis: The vast literature suggests various predisposing factors like areca nut/betel nut, tobacco, lime, malnutrition, immunological disorders, collagen disorders, capsaicin (A prime component in chillies), etc; association of areca nut catechu in the occurrence of Oral Submucous fibrosis has been proved by many studies.^{[26][27][28]} Commercially available economical sachets of gutka, paan contains areca nut cut in to small pieces coated with various chemicals and have strong association with this.^{[29][30]}

Areca nut (betel nut) chewing is ancient integral part of the religious and cultural rituals in many parts of Asia and in some pacific islands with two most important constituents are tannins (11%-12%) and alkaloids (0.15-0.67%) which is used in combination with other substances and available in various forms like uncured, cured, whole, broken, shredded, wafered and commercially manufactured.^[31] Based on biochemical studies of areca nut, four alkaloids have been conclusively identified: arecoline, arecaidine, guvacine and guvacoline, among which arecoline is the main agent. It has been suggested that arecaidine is an active metabolite in fibroblast stimulation and proliferation thereby inducing collagen synthesis. With the addition of slaked lime ($\text{Ca}(\text{OH})_2$) to areca nut in pan facilitates hydrolysis of arecoline to arecaidine making this agent available in the oral environment.

Tannin present in areca nut reduces collagen degradation by inhibiting collagenases. Thus it is found that fibrosis is induced as a combined effect of tannin and arecoline by the mechanism of reducing degradation and increased production of collagen respectively.^[32] Areca nut trigger the cells initially leading to excessive continuous abnormal accumulation of collagen, which is followed by a permanent change possibly in the fibroblast population. Trivedy C et al highlighted that copper upregulates collagen production in oral fibroblasts and copper in areca nut acts as a mediator of OSMF.^{[33][34]} Arakeri G et al found positive correlation between the incidence of OSMF and concentrations of copper in drinking water.^{[35][36]} The genotoxic effects of betel quid which are causing chromosomal instability leading to neoplastic process are assessed by easy, rapid and sensitive sister chromatid exchange (SCE) method. Rooban T et al analyzed that with chewing raw areca nut, there is increase in frequency and exposure time of increased salivary flow rate and pH respectively whereas in processed areca nut chewers, increase in duration and frequency of consumption increased salivary flow rate and decreased pH respectively.^[37]

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Awang MN et al and Jeng JH et al concluded in their studies that betel nut alkaloids and polyphenols are important carcinogens, while tobacco and slaked lime act as co-carcinogens.^{[38][39]} Sunali Khanna and Freny Karjodkar emphasized on the circulating immune complexes, serum copper, iron and selenium act as predictors for the occurrence and progression of precancer and cancer lesions and they concluded from their study that serum copper is raised from precancer to cancer transformation, serum iron and selenium levels is decreased in cancer.^[40] Rooban T et al evaluated the copper staining pattern of buccal epithelial cells in oral cytological smears of non-chewers, chewers, and OSMF and concluded that intense red staining of copper appeared as dark granules within cytoplasm in OSMF buccal smears as than in the chewers which indicates the role of copper in the etiopathogenesis of OSMF.^[41]

Mansi Ankolekar & Freny Karjodkar reported that a high level of copper in gutkha plays an initiating role in stimulation of fibrinogenesis by up regulation of lysyl oxidase and thereby increasing in cross linkage, inhibition of degradation of collagen and thereby causing its accumulation thus leading to OSMF. On the other hand, the high levels of iron in gutkha plays a key role in collagen synthesis, hydroxylation of proline and lysine, thus leading to decreased proline levels and increased hydroxyproline levels in the tissue.^[42] There is increase in serum copper level which causes an up regulation of the enzyme lysyl oxidase leading to cross linking of collagen and elastin in OSMF whereas serum iron level is not significantly altered as reported by Luquman M et al.^[43] Deficiency of Vitamin B12, folate and iron can affect the integrity of the oral mucosa. Significant haematological abnormalities have been reported in OSMF, including an increased blood sedimentation rate (ESR), anemia and eosinophilia, increased gamma globulin, a decrease in serum iron and an increase in total iron binding capacity (TIBC). Areca nut aggravates the increase in levels of proinflammatory cytokines and reduced anti-fibrotic IFN- γ in lamina propria which suggests that OSMF is an altered version of wound healing because the expression of various extracellular matrix molecules are similar to those seen in maturation of granulation tissue.^[32]

Matrix metalloproteinases (MMPs) are group of enzymes which together can degrade all the known components of extracellular matrix (ECM) which are expressed at very low levels in normal tissue.^[44] Increased and continuous deposition of extracellular matrix may take place as a result of disruption of the equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMP). OSMF fibroblasts produced more TIMP-1 protein than normal fibroblasts; mRNA expression of TIMP-1 in OSMF fibroblasts was also higher. Heparan sulphate proteoglycans (perlecan), fibronectin, Type III collagen and elastin appeared in the early and intermediate phases but there was complete replacement by collagen type I when the lesion progressed to an advanced phase. Tumor necrosis factor α (TNF- α) are cytokines which has pivotal role in transcription regulation of collagen and collagenase by increasing the proliferation of fibroblasts, collagen synthesis, collagenase production, and protease production and the balance among the mediators plays a key role in regulating the initiation and progression of scarring in fibrotic disease. Sodhi S et al conducted the case control study and found that plasma tumor necrosis factor α levels are significantly increased during inflammatory process of oral submucous fibrosis pathogenesis.^[8] Polymorphisms of the genes coding of G allele at position +49 of exon 1 for tumor necrosis factor-alpha (TNF- α) has been reported as a significant risk factor for OSMF. Tsai CH, Chou MY & Chang YC done the immunohistochemical study of cyclo-oxygenase (COX-2) in OSMF biopsy sections and found that there was an increased expression of the enzyme in moderate fibrosis which was disappeared in advanced fibrosis.^[32]

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Kaur J et al have reported the significant association between the increased expression of type I collagen and its chaperone, colligin, in OSMF lesions.^[45] Various studies suggest that collagen-related genes are altered by ingredients in the betel quid. A prominent mediator in OSMF is transforming growth factor-beta (TGF- β) which plays major role in wound repair and fibrosis. The genes CoL1A2, COL3A1, CoL6A1, COL6A3 and COL7A1 have been identified as definite TGF- β targets which are induced in fibroblasts at early stages of the disease. It was reported that anti- nuclear antibody (ANA) 23.9%, Smooth muscle antibody (SMA) 23.9% and gastric- parietal cell antibody (GPCA) 14.7% were positive in OSMF patients as compared to healthy control subjects. A recent study has revealed higher haplotype frequencies in pairs HLA B51/Cw7 and B62/Cw7 in OSMF patients and two new alleles were identified by sequencing-based typing as HLA DRB1-0903 and DRB1-1145.^[32]

All these findings are in favour of autoimmune role in OSMF etiopathogenesis. Rajendran R and Vidyarani highlighted that OSMF is having the family predilection and its tendency for familial linkage in their analysis of the family pedigrees with a positive history of fibrosis of eight families from Northern Kerala, South India.^[46] Nucleolar organizer regions (NORs) are loops of ribosomal DNA found in the nucleolus that can transcribe for ribosomal RNA associated with non- histone nucleoproteins which can be identified by silver staining (AgNORs) which denotes the proliferative activity and prognosis of lesions. AgNOR count is increased from normal mucosa to precancer to cancer, can be used to detect the degree of malignant potential in premalignant lesion and condition.^[47] Anita Balan and R Rajendran reported that there is significant progressive increase in AgNOR counts with increasing grades of OSMF and much more higher in coexisting carcinoma in their study.^[48] Various authors have reported the ischemic atrophy of the overlying epithelium in OSMF due to stromal changes, which undergoes progressive hyalinization, decrease in vascularity and cellularity, therefore epithelium become more prone to oral carcinogens and predispose to malignant trans-formation.^{[49][50]}

Clinical Features & Stages: Early OSMF includes a burning sensation in the mouth when consuming spicy food, appearance of blisters especially on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa.^[51] The most common initial symptoms of submucous fibrosis are burning sensation of the oral mucosa aggravated by spicy food (42%), followed by either hyper salivation or dryness of the mouth (25%).^{[52]:}

1. Blanching, i.e., marble-like appearance of the oral mucosa and stiffness of the oral mucosa.^[51]
2. Trismus (reduced mouth opening).^[53]
3. Burning sensation in the mouth when consuming spicy food.^[51]
4. Appearance of blisters especially on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa.^[54]
5. Reduced mobility of the soft palate and tongue.^[52]
6. Excessive salivation.^[52]
7. Defective gustatory sensation and dryness of the mouth.^[52]
8. Intolerance to eating hot and spicy foods.^[55]
9. Mild hearing loss due to blockage of Eustachian tube.^[55]

In advanced OSMF, oral mucosa becomes blanched and slightly opaque and white fibrous bands appear involving the buccal mucosa, lips, soft palate, faucial pillars and tongue. With progressive fibrosis, the stiffening of certain areas of the mucosa occurs difficulty in opening the mouth, inability

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to whistle or blow out a candle and difficulty in swallowing.^[52] In severe submucous fibrosis, the patient cannot protrude the tongue beyond the incisal edges and there is a progressive closure of the oral opening. In the myriad of literature available, numerous staging systems are put forward by various authors in the past. Some of the most important staging system which can routinely be used in the clinical practice, and help in early diagnosis and treatment includes: Haider SM, Merchant AT, Fikree FF, Rahbar MH (2000): Clinical and functional staging of OSMF:^[56]

Clinical Stages:

- Stage-I: -Faucial bands only.
- Stage-2: -Faucial and buccal bands.
- Stage-3: -Faucial, buccal, and labial bands.

Functional Stage:

- Stage-A: - Mouth opening >20mm.
- Stage-B: - Mouth opening 11-19mm.
- Stage-C: - Mouth opening <10mm.

Mathur RM and Jha T (1993) described the OSF staging based on clinical presentation:^[57]

- **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.

Management Protocol: OSMF has been a dilemmatic condition both in terms of its ill configured etiopathogenesis and confusion in management. Currently, much progress has been made in our understanding of its pathogenesis, which has encouraged us to formulate therapeutic strategies.

Cessation of Habit: The cessation of habit of eating betel quid, areca nut and other local irritants, spicy and hot food, alcohol and smoking through education and motivation is first step. The preventive measure should be in the form of total stoppage of the habit. Patients should be explained about the disease and abstention from chewing areca nut (Also known as betel nut) and tobacco. Minimizing consumption of spicy foods, including chilies, maintaining proper oral hygiene should be encouraged and the diet must be supplemented with foods rich in vitamins A, B complex, and C and iron.

Supplementary Care: Iron, vitamins and minerals rich diet should be advised to patients with oral submucous fibrosis. Various studies have implemented deficiency of iron both as a cause and effect in pathogenesis and etiology of OSMF. Hence routine hemoglobin levels followed by iron supplements should be give.^{[58],[59]}

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According to Martin and Koop,^[60] considered vitamin B deficiency to be important in the etiology of degenerative changes in oral mucosa before malignant transformation. Sirsat and Khanolkar,^[21] reported that the reaction caused by capsaicin in arousing a limited connective response was enhanced by vitamin B deficiency. Thus vitamin B complex administration may relieve glossitis, inflammation of tongue and cheilosis in OSMF patients. Several studies have confirmed the cancer preventive nature of antioxidants. The oral intake of retinoid has significant toxic effect in normal tissue. A less toxic group of micronutrients are carotenoids which include lycopene, its mode of action may involve stimulation of immune system or direct action in tumour cells. Lycopene also up regulates the lymphocytes resistance to stress and suppress the inflammatory response.^{[61],[62]}

Nidhi Thakur evaluated effectiveness of Micronutrients and Physiotherapy in the management of Oral Submucous Fibrosis in 64 patients with oral submucous fibrosis. Mouth opening in patients showed significant improvement at the end of 6 weeks as compared to the initial mouth opening.^[63] Another study by (Maher et al) evaluated the efficacy of combination of micronutrients (Vitamins A, B complex, C, D, and E) and minerals (iron, calcium, copper, zinc, magnesium, and others) in controlling the symptoms and signs of OSMF.^[64] Significant improvement in symptoms, notably intolerance to spicy food, burning sensation, and mouth opening, was observed at exit. Borle et al,⁽¹⁸⁾ reported that Vitamin A, 50,000 IU chewable tablets, if given once daily could cause symptomatic improvement. Trismus (Tonic spasm of masticatory muscles) did not improve with this treatment.^[65]

Steroid Therapy: Steroids inhibit the proliferation of fibroblasts and this cause reduction in the number of collagen fibers. They also act to release cellular proteases in the connective tissue extracellular compartment which in turn activate the collagens and zymogen that ingest the insoluble collagen stimulating the rate of collagen breakdown. They also act by inhibiting the inflammatory response.^[58] Steroid ointment is applied topically in the cases with ulcer and painful oral mucosa. It is a common practice in India to treat OSMF patient using intra lesional dexamethasone injection. In OSMF the oral mucosa is already atrophied and inflamed. By using intra lesional method, there be following disadvantages: 1) More discomfort to patient 2) Needle trauma may heal by fibrosis. The various problems associated with intralesional injection could be solved by atraumatic method of drug delivery system like mucosal patch.^[66] A Therapy with hydrocortisone 25 mg tablet, in doses of 100mg/day is useful in relieving burning sensation. This is supplemented with local injection of hydrocortisone 25mg at biweekly intervals at the affected site. Increased vascularity of the site is observed, which is due to fibrinolytic, anti-allergic and anti-inflammatory action of corticosteroid.^[67]

Hyaluronidase: The combination of steroids and Hyaluronidase shows better long term results than either agent used alone (Kakar 1985). It produces burning sensation and trismus. It acts by breaking down hyaluronic acid, lowers the viscosity of intracellular substances and decreases collagen formation.^[68] It breaks down hyaluronic acid (Ground substance of connective tissue), lowers the viscosity of intracellular cement substance i.e. Hyaluronidase decreases cell formation by virtue of its action on hyaluronic acid, which plays an important role in collagen formation.^[67] In a study by Singh M et al on 100 patients of OSMF and used hydrocortisone and triamcinolone respectively in two groups. No statistically significant difference in symptom score, sign score and histopathological improvement was seen between the two groups. Treatment regimen of group B was more convenient to the patients because less number of visits required and cheap. No side effects were seen.^[69]

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Pentoxifylline: Rajendran et al had tried earlier Pentoxifylline as treatment in patients with OSMF and reported good results.^[70] Pentoxifylline is a tri substituted methyl methylxanthine derivative. It is termed as rheological modifier; it improves micro circulation and decreased platelet aggregation as well as granulocyte adhesion. Haddad et al treated 34 radiation induced superficial fibrotic lesions of skin with Pentoxifylline and vitamin E for 3 months and reported a significant improvement in radiation induced fibrosis.^[71] Rawlins et al reported that Pentoxifylline has a direct effect on inhibiting burn scar fibroblasts.^[72] Extrapolating this finding, the drug has been also used to alleviate the symptoms in patients with OSMF. There are both central nervous system and gastrointestinal system side effect which are dose related and therefore minimized by dose reduction. The biologic activities of Pentoxifylline includes increasing red cell deformability, leukocyte chemotaxis, antithrombin and anti- plasmin activities, and more importantly to the present context, its fibrinolytic activity.^[70] Pentoxifylline decreases red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and whole blood viscosity.^[73]

Placental Extracts: Placental extract accelerates cellular metabolism, aids in absorption of exudates, and stimulates regenerative process, increases physiological function of organs, produces significant enhancement of wound healing and it has anti-inflammatory effect. Its use is based on the method by: tissue therapy introduced by Filatov in 1933, later in 1953. His theory states that animal and vegetable tissue, when severed from parent body and exposed to conditions unfavorable but not mortal to their existence undergo biological re adjustments leading to development of substance in state of survival to ensure their vitality such tissue are the extract, implanted or injected in to the body after resistance to pathogenic factors stimulate the metabolic or regenerative processes, thereby favoring recovery. It has no contra indications and results are obtained to be lasting.^[74] It is injected around fibrous bands, intra-muscularly, at the interval of 3 days for 15 days and each time 2 ml solution is deposited.^[67] Katharia S. K. Singh S. P. K Kulshretra V. K. studied the effect of placenta extract in management of Oral submucous fibrosis and stated that there was significant improvement in mouth opening, colour of oral mucosa and reduction of fibrous bands.^[75] Sudhakar Vaidya, V K Sharma got good results with injection of placental extract intra lesion ally associated with antioxidants and jaw dilator exercises has been found useful in 52 cases.^[55]

Interferon-Gamma: This plays a role in treatment of patients with OSMF because of its immunoregulatory effect. Interferon-Gamma is also known as anti-fibrotic cytokine, patients treated with an intralesional injection of interferon gamma experienced improvement of symptoms. Haque MF et al found significant improvement in interincisal distance, reduced burning sensation and increased suppleness oral mucosa by 8 weeks of twice a week intralesional injection of 50 mg / 0.25 ml of interferon gamma.^[76] Interferons are a family of proteins and glycoproteins which are closely related to cytokines and they are immunoregulatory peptides that were first described as inhibitors of viral replication and later recognized as regulators in the immune system. Interferon- γ is also known as the antifibrotic interferon which leads to reduction in collagen synthesis.^[77]

Turmeric: Administration of turmeric powder offers protection benzopyrene induced increase in micro nuclei in circulating lymphocytes and its excellent scavenger of free radical in vitro. Turmeric oil and turmeric oleoresin both act synergistically in vivo to offer protection against DNA damage.^[78] *Curcuma longa* Linn is commonly known as Haldi, Turmeric or Indian saffron belongs to family

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Zingiberaceae. Ramsewk et al described in their study the cytotoxic, anti-inflammatory and antioxidant activity of curcumin I, II and III from *Curcuma longa*.^[79] Das DA et al inferred from their study that curcumin and turmeric oil is beneficial, affordable, noninvasive herbal therapy for OSMF.^[80] In one clinical trial alcoholic extracts of turmeric 3g, turmeric oil 600 mg and turmeric oleoresin 600 mg, when consumed orally, decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes in OSMF.^[78]

Immune Milk: Immune milk contains an anti-inflammatory component that may suppress the inflammatory reaction and modulate cytokine production. Symptomatic relief in patients may be partially attributed to mice nutrients contained in the immune milk powder ^[81]

Oral Mucoadhesive Drugs: Mucoadhesive systems for oral local drug delivery include adhesive tablets, adhesive patches, adhesive films or pellicles, adhesive semisolid systems (Gels, ointments), and adhesive liquid systems (Sprays, mouthwashes).^[82] Kumar NS et al reported semisolid mucoadhesive curcumin gel having antitumorigenic and antimutagenic property can be used for the treatment of oral sub mucous fibrosis which provides effect for extended periods of time.^[83] Averineni RK et al conducted a preliminary study to develop mucoadhesive buccal films of valdecoxib a novel COX-2 inhibitor for the treatment of oral sub-mucous fibrosis.^[84] Sudarshan R et al reported that aloe vera reduces burning sensation and improves mouth opening when applied topically in mild stage clinically and early stage histopathologically of OSMF in comparison to antioxidants from their study. It is safe, noninvasive, economical, easily available and efficient in the treatment of OSMF.^[85] Alam S et al reported that aloe vera gel was effective as an adjuvant therapy in treatment of OSMF.^[86] Spirulina is a microalgae which contains phenolic acid, tocopherols, beta carotene and have potent antioxidant properties. Shetty P et al suggested that 500mg spirulina twice daily can be used as an adjuvant therapy in the initial management of OSMF.^[87]

Surgical Treatment: The various surgical modalities chosen according to the stage of clinical progression to gain maximal interincisal distance (ID) includes the excision of fibrotic tissues and covering the defect with split-thickness skin, fresh human amnion, or buccal fat pad (BFP) grafts.^[88] J. N. Khanna, N. N. Andrade treated advanced cases by a new surgical technique of a palatal island flap based on the greater palatine artery in combination with temporalis myotomy and bilateral coronoidectomy.^[89] Bande CR et al have done the comparative study of extended nasolabial flap with the platysma myocutaneous muscle flap for reconstruction of intraoral defects after release of oral submucous fibrosis and revealed that both procedures are equally effective in management, but extra oral scar was not aesthetically acceptable in the nasolabial group.^[90] Le PV et al suggested that oral stent can be used as an adjunct to prevent surgical relapse.^[91]

Early and postoperative rehabilitation is the most important factor in maintaining the intraoperative interincisal distance therefore psychologic preparation of the patient before surgery plays a significant role in the success of surgery. Huang IY et al highlighted that patient compliance is very essential to prevent the post-operative surgical complications which includes patient motivation, the nature and chronicity of the disease, treatment variables, and the quality of the patient- doctor relationship.^[92] The stem cell intralesional injections therapy improves the blood circulation. Sankaranarayanan S et al injected autologous bone marrow stem cells in 38 year old male patient with oral submucous fibrosis which showed significant improvement in blanching, fibrous

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bands and mouth opening, 4 weeks after injection.^{[93][94]} Stephen Cox & Hans Zoellner conducted a clinical trial of physiotherapeutic treatment to improve oral opening in oral submucous fibrosis in the Nepali population and suggested that physiotherapy is effective for increasing the oral opening and can be readily used to improve OSF in communities with otherwise limited health resources.^[95]

Talsania JR et al evaluated the efficacy of Laser with follow-up physiotherapy to reduce trismus in OSMF and concluded that Diode laser is a less expensive and an alternative method in Asian population as it requires less hospital stay and less follow up as compared to other surgical methods.^[96] CO2 lasers are predefined rather than a scalpel or technique involving multiple tiny incisions for surgical relief of limited oral aperture because the laser beam spontaneously seal all the blood vessels, allowing the surgeon perfect visibility and accuracy in excising fibrous tissue.^[97]

CONCLUSION: No complete success has been achieved because of unpredictable etiology, immune response or immune status of individual patient, and pro and cons of every treatment modality depending on the stage of the OSMF. After having a glance over the vast literature on OSMF, it is said that there is hope for further detail evaluation for management of OSMF for having better outcome results to the patients suffering from this precancerous condition.

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