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REVIEW ARTICLE

Oral Submucous Fibrosis- Current Concepts of Aetiology & its Management

Manas Gupta[1],Pankaj Mishra[2],Kirti Shrivastava[3],Neha Singh[4],Pushpraj Singh[5]

[1,3,4]Assistant Professor,Departmeent Of Oral Medicine and Radiology,Rishiraj College Of Dental Sciences,Bhopal

[2]Asst. Professor,Department Of Conservative and Endodontics,,Rishiraj College Of Dental Sciences,Bhopal

[5]Lecturer, Departmeent Of Oral Medicine and Radiology,Rishiraj College Of Dental Sciences,Bhopal

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ABSTRACT

Oral submucous fibrosis (OSMF) is a potentially malignant disorder and crippling condition of oral mucosa. It is a well-recognized chronic insidious disease, precancerous condition, autoimmune and collagen related disorder which is multifactorial in origin associated with betel quid chewing characterized by progressive hyalinization of the lamina propria. In the vast literature available for OSMF, numerous staging systems are put forward by various authors in the past. Some of the most important staging system are being routinely used in the clinical practice, and has helped in early diagnosis and treatment. The management of oral submucous fibrosis has been the subject of controversy ever since Schwartz first described the condition in 1952. An attempt is made to analyze critically and update the knowledge of the recent developments that enhances the understanding of the aetiology of this premalignant condition and its medicinal & surgical management which improves the life expectancy.

INTRODUCTION:

Oral submucous fibrosis (OSMF) is a chronic, progressive, disabling, scarring, precancerous condition of the oral mucosa which was first described by Schwartz in 1952 among five East African women of Indian origin under the term atropica idiopathica (tropica) mucosae oris.[1, 2, 3, 4] In 1966, Pindborg defined oral submucous fibrosis as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating". [1] 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] 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 also found in other South-Asian countries like Bangladesh, Sri Lanka, Pakistan, Taiwan, Southern China, Polynesia and Micronesia.[1,4,5] Pindborg JJ has analyzed the epithelial changes in 156 biopsy samples of 118 patients and suggested that submucous fibrosis should be considered as a precancerous condition.[6] There is increase in disease among young generation due to increased use of commercially prepared areca nut (pan masala) which is easily access, effective price changes and marketing

* *Corresponding author. Senior Lecturer; Department of Oral Medicine & Radiology, Rishiraj College of Dental Sciences & Research Centre, Bhopal (M.P)*

Contact number: 08964920653 Email id: drmanasg@gmail.com

strategies in India[1]. The malignant transformation rate of OSMF was found to be 7.6% in an epidemiological survey of oral cancer and precancerous lesions in rural Indian population.[7]

Pindborg and Sirsat reported that onset of disease is insidious and often 2 to 5 years of duration. The earliest clinical sign is blanching giving marble like appearance of oral mucosa which may be localized, diffused or in the reticular (lace) like pattern. The oral mucosa is involved symmetrically in most of the cases, buccal mucosa and lips are affected at an early stage although previously it was thought that the palate and the faucial pillars are involved first. The most common initial symptom is burning sensation of oral mucosa which is aggravated by spicy food. The periods of exacerbation manifested as vesiculation, ulceration, pigmentation changes, dryness of mouth, depapillation of tongue. Gingiva become fibrotic, depigmented with loss of stippling. As the disease progresses gradual stiffening of oral mucosa with tough and leathery consistency associated with fibrous bands in the buccal mucosa which run in a vertical direction involving the tissue around the pterygomandibular raphae that causes varying degrees of difficulty in mouth opening. In severe labial involvement, the opening of the mouth is altered to an elliptical shape. Similarly when soft palate is involved it appears as a heavy curtain is hanging from the hard palate and uvula become shrunken which appears as bud shape. In severe cases of fibrosis involving tongue and buccal mucosa causes difficulty in eating, blowing, whistling and sucking. In advanced cases involvement of oesophagus and eustachian tube leads to difficulty in swallowing food, referred pain to ears and deafness and nasal voice have been noticed.[3, 8, 9, 10, 11]

In the vast literature available for OSMF, 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: [12]

Clinical stage:

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

Functional stage:

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

Mathur RM and Jha T (1993) described the OSF staging based on clinical presentation: [13]

Stage-1: Early OSF:

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 OSF:

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 OSF:

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.

ETIOPATHOGENESIS:

When OSMF was first described in 1952, it was classified as an idiopathic disorder.[14] Later on various researchers put forward many hypothesis suggesting that OSMF is multifactorial origin with possible aetiological factors to date are areca nut, capsaicin in chilies, micronutrient deficiencies of iron, zinc and essential vitamins. In addition, a possible autoimmune basis to the disease with demonstration of various auto-antibodies and an association with specific HLA antigens has also been proposed.[1, 7] Based on various reported literature we are summarizing the etiopathogenesis of OSMF as mentioned in Table:1.

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.[15] 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 ($Ca(OH)_2$) 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.[14]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.[3] Trivedy C et al highlighted that copper upregulates collagen production in oral fibroblasts and copper in areca nut acts as a mediator of OSMF. [16, 17]

Arakeri G et al found positive correlation between the incidence of OSMF and concentrations of copper in drinking water and concluded from their study that OSMF may affect people in developing countries and those of low socio-economic status because drinking water can be contaminated with copper (and other trace

elements) which should be considered to be an important contributing factor. To reduce its incidence, high standards of drinking water must be maintained, and they recommend that all public water supplies meet those set out in the National Primary Drinking Water Regulations.[18, 19]

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.[9] Rooban T el 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. For chewers with betel quid with tobacco, increase in duration was significantly associated with decrease in salivary pH. He concluded that resting whole mouth salivary flow rate (SFR) and pH are altered in arecanut chewers, rendering the oral mucosa vulnerable to the toxic effects of arecanut.[20] 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.[21,22]

OSMF is basically a collagen disorder. Hydroxyproline is an aminoacid found only in collagen which is present in hydroxylated form of 4 hydroxyl proline and require ferrous iron and ascorbic acid for reaction. The decreased iron levels may be due to utilization in the fibrosis process.[4] Sunali Khanna and Freny Karjodkar emphasized on the circulating immune complexes, serum copper, iron and selenium act as a 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.[23]

High copper content in areca nut plays a vital role in pathogenesis of OSMF. 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 .[24]

Mansi Ankolekar & Freny Karjodkar reported that a high level of copper in gutkha plays an initiating role in stimulation of fibrinogenesis by upregulation of lysyl oxidase and there by 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.[25] There is increase in serum copper level which causes an upregulation of the enzyme lysyl oxidase leading to cross linking of collagen and elastin in OSMF where as serum iron level is not significantly altered as reported by Luquman M et al.[26]

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).[9]

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.[14] 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.[27] 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.[14] The immunohistochemical staining of formalin fixed, paraffin embedded tissue sections of OSMF case study done by Rajendran R et al and they reported that there is significant increase in the levels of stromal expression of MMP-1, MMP-2 and MMP-9 and TIMP-1 and TIMP-2 by using monospecific antibodies reacting against tissue antigens in their study.[27]

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 scaring 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.[5] 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.[14]

Colligin / HSP 47 is a 47 K Da stress protein which acts as chaperone for collagen. Kaur J et al have reported the significant association between the increased expression of type I collagen and its chaperone, colligin, in OSMF lesions.[28] Various studies suggest that collagen-related genes are altered by ingredients in the betel quid.[1] A prominent mediator in OSMF is transforming growth factor-beta (TGF-β) which plays major role in wound repair and fibrosis.[7] 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.[1] 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.[9, 14] 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. They also suggested that relationship between OSMF risk and the number of putative high risk genotypes should be evaluated for the collagen-metabolizing and cross-linking pathways which are involved in causation and biologic progression of OSMF.[29]

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. AgNOR method can be used as simple, reproducible, prognostic indicator, reproducible with pretherapeutic assessment of biologic aggressiveness of the disease.[9, 30, 31] 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.[31]

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 transformation.[32,33] Rajendran R et al have done the quantitative assessment of the mucosal vascularity in oral submucous fibrosis by image analysis using OPTIMAS ver 6.0 software and concluded that vascular dilatation is an adaptive response to compensate tissue ischaemia / hypoxia .[33] Rajendran R and Shirley Varkey have done the morphological assessment of the nature of vascularity in OSMF mucosa by immunohistochemical study of inducible nitric oxide synthase (iNOS) and observed the significant vasodilation due to upregulated iNOS which act as a net vasodilator.[32]

Ning Li et al done the pilot immunohistochemical study of each gene in 66 OSMF patients and the microarray analysis showed that 661 genes were up-regulated and 129 genes were downregulated in OSMF, among that the top three up-regulated genes are Loricrin, Cartilage oligomeric matrix protein (COMP), Cys-X-Cys ligand 9 (CXCL9) and the top two downregulated genes are keratin 19 (KRT19), cytochrome P450 3A5 (CYP 3A5). Based on above mentioned study these five novel genes plays important role in the pathogenesis of OSMF and can be used as biomarkers for early detection of OSMF.[34] Cheng-Kuang Lee et al analyzed 44 OSMF cases for real time OSMF diagnosis with the help of swept-source optical coherence tomography (SS-OCT) system and specially designed probe by measuring epithelium (EP) thickness and standard deviation (SD) of A-mode scan intensity in the laminar propria (LP) layer.[56] Hsin-Ming Chen et al reported that OSMF mucosa has a very unique pattern of auto-fluorescence spectrum and can be used as reliable tool for chairside investigation for clinical diagnosis.[58] Based on various researches we are summarizing that OSMF is chronic irreversible disease due to genetic alteration of fibroblast, but exact etiology is unknown and the possible etiopathogenesis of OSMF are mentioned below: [9]

1- Areca nut chewing stimulates fibroblasts proliferation which increases collagen production
2- OSMF tissue secretes fibrogenic cytokines by activated macrophages and T lymphocytes
3- OSMF fibroblasts leads to decreased secretion of collagenase and collagen phagocytosis
4- Collagen cross linkage by fibroblast is increased by the upregulation of lysyl oxidase in OSMF fibroblasts
5- OSMF fibroblast produce more stable type I collagen trimer which are stabilized by catechin and tannins produced from the areca nut

PRECANCEROUS NATURE & MALIGNANT TRANSFORMATION:

The precancerous nature of oral submucous fibrosis was first mentioned by Paymaster in 1956. Unlike other potentially malignant disorders, it is irreversible which either remain stationary or become severe with high risk of oral cancer development due to denuded or atrophic oral mucosa vulnerable to carcinogens. Pindborg in 1972 summarized the criteria in support of the precancerous nature of this disease as higher prevalence of leukoplakia among OSMF patients, high frequency of epithelial dysplasia, concurrent finding of submucous fibrosis in oral cancer patients, histological diagnosis of carcinoma without the clinical suspicion of it and incidence of oral cancer among patients with submucous fibrosis.[3, 10] OSMF has a malignant transformation rate of 7–30%. Pathogenesis is thought to be multifactorial. The genotoxic and mutagenic effects of areca nut are attributed to polyphenols, alkaloids, and areca-nut-specific nitrosamines such as N-nitrosoguvacoline, N-nitrosoguvacine, 3-(N nitrosomethylamino) propionaldehyde, and 3-(Nnitrosomethylamino) propionitrile. Recently, a loss of heterozygosity in 23 "hotspot" loci which alter genes that control the cell cycle has been recognised as an important molecular marker for malignancy in OSMF.[34]

MANAGEMENT:

Historically, OSMF has been an enigmatic condition both in terms of its poorly understood etiopathogenesis and difficulty in management. Recently, however, much progress has been made in our understanding of its pathogenesis, offering insights into therapeutic strategies. As the exact causative factor for OSMF is a matter of conflict, the failure to achieve proper or specific treatment for it may be reason for its incomplete

regression. Stoppage of areca nut chewing is foremost important measure to treat OSMF. Various drugs alone or in combination are used to treat this crippling disease as summarized in Table: 2**.**

Chewing Betel Quid is considered an important etiological factor of OSMF because of the excessive reactive oxygen species (ROS) induced by the ingredients of BQ.[35] Lycopene is a major carotenoid found in tomato which have chemopreventive properties against oral potentially malignant disorders by its antioxidant and anti-inflammatory activity.[36, 37] Selvam NP et al suggested that lycopene in combination with intralesional steroids and hyaluronidase is highly efficient in mouth opening and reducing other symptoms.[38] Karemore T V et al and Sunderraj S et al concluded that lycopene gives significant relief from signs and symptoms of OSMF in their studies.[39, 40] Gupta S et al in their study found that after 6 weeks of treatment with tablets containing mostly beta-carotene and vitamin E, patients showed an effective increase in mouth opening and tongue protrusion.[41] Anil Kumar & Sharma SC concluded that either oral zinc alone or in combination with oral vitamin A in grade I & II patients and oral zinc with local cortisone in grade III patients of OSMF may be employed in future to treat OSMF.[42] Rao PK reported that use of alpha lipoic acid along with intralesional steroid injections therapy have beneficial impact.[43] Tai YS, Liu BY et al in their study stated the use of oral administration of milk from cows immunized with human intestinal bacteria which leads to significant improvement of symptoms and signs in OSMF patient.[44]

Several glucocorticoids are used for the treatment of OSMF such as short-acting (hydrocortisone), intermediate acting (triamcinolone), and long-acting glucocorticoids (betamethasone and dexamethasone). They act by their anti-inflammatory activity by inhibiting the generation of inflammatory factors and increasing the apoptosis of inflammatory cells. Thereby partially relieving the patients of their symptoms at an early stage of OSF. Therefore steroids are useful in controlling symptoms, or as an adjunct therapy.[35]A combination of Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks. Currently, intralesional steroids are the main treatment modality. These are injected into the fibrotic bands biweekly for 6–8 weeks along with mouth-opening exercises.[45]

Placentrex is an aqueous extract of human placenta that contains nucleotides, enzymes, vitamins, amino acids, and steroids. It acts by biogenic stimulation and increasing the vascularity of tissues based on the principle of tissue therapy introduced by Filatov in 1933.[46] Katharia SK reported that placenta extract when administered result in significant improvement in mouth opening, color of mucosa, burning sensation, and reduction of fibrotic bands.[47]

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.[48] Interferon-ϒ is also known as the antifibrotic interferon which leads to reduction in collagen synthesis. Haque MF et al conducted a study to observe the effect of IFN- ϒ on collagen synthesis by OSMF fibroblasts in vitro and efficacy of intralesional injections of interferon gamma. They 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.[49]

Collagenase is a lysosomal enzyme, capable of degrading phosphate esters, proteins, polysaccharides, glycosides, and sulfate esters. In a controlled clinical trial, Lin and Lin found that intralesional injections of collagenase resulted not only in significant improvement in mouth-opening, a striking reduction of hypersensitivity to spices, sour, cold, and heat. Hyaluronidase also showed a much quicker effect in ameliorating the burning sensation and painful ulceration than did dexamethasone, though the effect was short-term. It acts by depolymerizing hyaluronic acid, which is the ground substance in connective tissue, lowering the viscosity of the intercellular cement substance, and decreasing collagen formation. Chymotrypsin, an endopeptidase, hydrolyzes ester and peptide bonds and is also also used as a proteolytic and anti-inflammatory agent in the treatment of OSF.[35]

Pentoxifylline is a methylxanthine derivative that has vasodilating properties and increases the mucosal vascularity. The curative effect of pentoxifylline may be attributable to its properties of suppressing leukocyte function, altering fibroblast physiology, and stimulating fibrinolysis.[35] Rajendran R et al suggested pentoxifylline (Trental) 400 mg 3 times daily for 7 months as an adjunct therapy for OSMF .[50] Jigre V et al conducted a comparative study of levamisole and antioxidant therapy and highlighted that alone 50 mg levamisole three times daily for three alternate weeks showed significant improvement in mouth opening and reduction in burning sensation.[51] Colchicine inhibits collagen synthesis by disruption the microtubule formation and depolymerizes microtubules which prevent the extrusion of collagen fibers from the fibroblast and increases collagenolytic activity.[52] Krishnamoorthy B et al reported that colchicine orally 0.5 mg twice daily along with intralesional 0.5 ml hyaluronidase 1,500 IU gives significant improvement in burning sensation and mouth opening.[53]

Curcuma longa Linn. is commonly known as Haldi, Turmeric or Indian saffron belongs to family Zingiberaceae. Mishra et al reported that the volatile oil of Curcuma longa has effective anti-inflammatory and anti-hyaluronidase action. They suggested the antioxidative effect as evidenced by inhibition of diffusion capability of the hyaluronidase enzyme by the oil. Ramsewk et al described in their study the cytotoxic, anti-inflammatory and antioxidant activity of curcumin I, II and III from Curcuma longa. [54] Das DA et al inferred from their study that curcumin and turmeric oil is beneficial, affordable, non invasive herbal therapy for OSMF.[55] In one clinical trial alcoholic extracts of turmeric 3 g, 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.[45,56] Tea

pigments are oxidized products of polyphenols, derived from tea leaves that could improve microcirculation and hemorrheology. After administering tea-pigment tablets in the treatment of OSF, Li and Tang found an overall effective rate and believed that tea pigment's acts by decreasing high blood viscosity, improving microcirculation, and increasing the activity of superoxide dismutase.[35]

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, non invasive, economical, easily available and efficient in the treatment of OSMF.[57] Alam S et al reported that aloe vera gel was effective as an adjuvant therapy in treatment of OSMF. [58] Spirulina is a microalgae which contains phenolic acid, tocopherols, beta carotene and have potent antioxidant properties. Shetty P et al suggested that 500 mg spirulina twice daily can be used as an adjuvant therapy in the initial management of OSMF.[59]

Oral mucoadhesive drug delivery is very efficient therapeutic targeted drug approach than systemic delivery, as smaller amounts of drug can be easily dispersed at the site of the disease, thereby reducing its side effects. 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). [60] Kumar NS et al reported semisolid mucoadhesive curcumin gel having antitumeric and antimutogenic property can be used for the treatment of oral sub mucous fibrosis which provides effect for extended periods of time.[61] 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. [62]

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. [63] 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.[64] 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.[65] Le PV et al suggested that oral stent can be used as an adjunct to prevent surgical replase.[66] 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.[67]

With the advancements in medical and dental treatment protocol, the stem cell intralesional injections therapy which 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 bands and mouth opening, 4 weeks after injection.[68,69] 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.[70] 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.[71]

CONCLUSION:

As long time span of time has been passed since first diagnosis of OSMF and treatment given for it till this era no definite outcome came out. Based on available literature which indicates the main aetiological factors for OSMF are the constituents of areca nut, mainly arecoline, whilst tannin may have a synergistic role. These chemicals appear to interfere with the molecular processes of deposition and / or degradation of extracellular matrix molecules such as collagen, causing imbalance in the normal process. Although the above mechanisms may explain the induction, maintenance and progression of fibrosis in OSMF, further research is required in order to identify the mechanism leading to carcinogenesis in this fibrotic oral mucosa. 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. The individual mechanisms operating at various stages of the disease namely the initial, intermediate and advanced need further study in order to propose appropriate therapeutic interventions.

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TABLES AND FIGURES

Table 1- Etiopathological Factors of OSMF:

Etiopathological Factors	Role
1- Areca nut - Arecoline, Arecaidine, Guvacine,Guvacoline	Stimulation and proliferation of fibroblast
Tannin	Reduces collagen degradation by inhibiting collagenases
Copper	Upregulation of the enzyme lysyl oxidase leading to cross linking of collagen and elastin
Iron	High levels of iron causes hydroxylation of proline and lysine in collagen synthesis
2- Nutritional deficiency of Iron, Folate & Vitamin B12	Disruption of integrity of oral mucosa leading to increase susceptibility to carcinogens
3- High intake of Chillies	Capsaicin causes hypersensitivity reaction to oral mucosa which stimulates fibrosis
4- Enzymes: Matrix metalloproteinases (MMPs)	Increased and continuous deposition of extracellular matrix due to disruption of the equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMP)
5- Cytokines: Tumor necrosis factor α (TNF- α) ; Interleukin 6 (IL-6); Interferon alpha (IF-α)	Regulating the initiation and progression of scaring in fibrosis
6- Colligin / HSP 47	Colligin / HSP 47 is a 47 K Da stress protein which acts as chaperone for collagen and increased along with type I collagen
7- Transforming growth factor-beta (TGF-β)	A prominent mediator in collagen production by activation of procollagen genes; elevation of procollagen proteinases levels: (a) procollagen C-proteinase (PCP) / bone morphogenetic protein1 (BMP1) (b) procollagen N-proteinase (PNP) and up-regulation of lysyl oxidase (LOX) activity
8- Nucleolar organizer regions (NORs)	Nucleolar organizer regions (NORs) are loops of ribosomal DNA identified by silver staining (AgNORs) which denotes biologic aggressiveness of the disease
9- Inducible nitric oxide synthase (iNOS)	Increased vasodilation due to upregulated iNOS
10- Up-regulated and Down-regulated genes	Up-regulated genes are Loricrin, Cartilage oligomeric matrix protein (COMP), Cys-X-Cys ligand 9 (CXCL9) and Downregulated genes are keratin 19 (KRT19), cytochrome P450 3A5 (CYP 3A5)

Table 2: Various drugs alone or in combination are used in OSMF management

1	Betel quid	Cessation of habit Patient motivation, the nature and chronicity of the disease, treatment variables, and the quality of the patient-doctor relationship	Prevent excessive reactive oxygen species (ROS) induced by the ingredients of betel quid
2	Nutritional Supplement: Vitamin A, B complex, C, D and E, Iron, Copper, Calcium, Zinc, Magnesium and Selenium	Micronutrients and minerals	Vitamin A & B- growth and repair of epithelial tissues. Vitamin C-work together to boost metabolism and immune system. Beta carotene-increasing the number of circulating lymphocytes and T helper cells which improves cellular immunity Zinc acts as an epitheliazing agent Copper- Induce lysyl oxidase activity, Up-regulation of collagen synthesis by fibroblasts, Inhibition of collagen degradation
3	Lycopene	Lycopene-8 mg twice a day for 2 months	Potent radical scavenger and has highest singlet oxygen and free radicals quenching capacity.
4	Steroid- Topical / Intralesional- Short-acting (hydrocortisone), Intermediate acting (triamcinolone), Long-acting glucocorticoids (betamethasone and dexamethasone)	Intralesional steroids are the main treatment modality. These are injected into the fibrotic bands biweekly for 6–8 weeks along with mouth-opening exercises.	It acts by their anti-inflammatory action by inhibiting the generation of inflammatory factors and increasing the apoptosis of inflammatory cells
5	Placentrex	Intralesional injection of 2ml Placental extract (Inj.Placentrex) once a week for one month.	It acts by biogenic stimulation which increases the vascularity of tissues based on the principle of tissue therapy
6	Interferon	8 weeks of twice a week intralesional injection of 50 mg / 0.25 ml of interferon gamma.	Interferon-ϒ is also known as the antifibrotic interferon which leads to reduction in collagen synthesis Effects on collagenous production and cell proliferation Increases synthesis of collagenase
7	Collagenase Enzyme-Hyaluronidase	1500 IU	It acts by depolymerizing hyaluronic acid, which is the ground substance in connective tissue, lowering the viscosity of the intercellular cement substance, and decreasing collagen formation.
8	Chymotrypsin	Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks.	It hydrolyzes ester and peptide bonds and is also used as a proteolytic and anti-inflammatory agent
9	Pentoxifylline	Trental-400 mg 3 times daily for 7 months	It has vasodilating properties and increases the mucosal vascularity. suppressing leukocyte function, altering fibroblast physiology, and stimulating fibrinolysis.
10	Buflomedil hydrochloride	450 mg per day along with steroids and vitamins	It acts as vasoactive agent which reduces ischemic effect and increases nutritional and therapeutic effect reaching to the tissues
11	Nylidrin hydrochloride	9-24 mg/day in 4 divided doses.	It acts as a peripheral vasodilator and

			sympathomimetic agent which dilates/ relaxes blood vessels, ensuring greater blood supply to the ischemic tissue.
12	Levamisole	50 mg TDS for 3 alternate weeks	It act as immunomodulatory drug which modifies both cellular and humoral immunity; Modulate inflammatory cytokines also.
13	Colchicine	0.5 mg twice daily	It inhibits collagen synthesis by disruption the microtubule formation and depolymerizes microtubules which prevent the extrusion of collagen fibers from the fibroblast and increases collagenolytic activity.
14	Cow milk immunized with human intestinal bacteria	45 g milk powder twice a day for 3 months	It has anti-inflammatory action and modulate cytokine production
15	Curcuma longa Linn (Turmeric)	Alcoholic extracts of turmeric (3g), turmeric oil (600mg), turmeric oleoresin (600mg), daily for 3 months .	It has anti-inflammatory, anti-hyaluronidase and antioxidative effect by inhibition of diffusion capability of the hyaluronidase enzyme by the oil
16	Tea pigments	Oxidized products of polyphenols, derived from tea leaves.	It acts by decreasing high blood viscosity which improves microcirculation, and also increases superoxide dismutase activity
17	Aloe vera	70 mg gel/packet	It acts as wound healing hormone and serols in the Aloe vera have strong anti-inflammatory effect
18	Spirulina	500 mg twice daily	It is a microalgae which contains phenolic acid, tocopherols, beta carotene and have potent antioxidant properties.
19	Physiotherapy	Manual stretching Rubber plugs Tongue blades Thera Bite apparatus	5 times daily physiotherapy by interpositioning tongue spatulas between teeth and adding a new spatula every 5–10 days for 4 months
20	Laser therapy	Laser with follow-up physiotherapy	It has less morbidity and is suitable for Asian population as it requires less hospital stay and less follow up as compared to other surgical methods.
21	Surgical therapy	Buccal fat pad Collagen graft Nasolabial flap Superficial temporal flaps Tongue flaps Palatal mucoperiosteal flap Amniotic graft Split thickness skin graft Bilateral radio artery forearm free flap	Patient compliance is very essential to prevent the post operative surgical complications. Oral stent can be used as an adjunct to surgery to prevent relapse
22	Stem cell therapy	Intralesional autologous bone marrow stem cells	It improves the blood circulation of tissues