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Oral Submucous Fibrosis- A review

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Abstract:
Oral Submucous fibrosis (OSMF) has traditionally been described as "a chronic, insidious, scarring disease of the oral cavity, often with the involvement of the pharynx and the upper esophagus". Millions of people are impacted, particularly in countries in South and South East Asia. Chewing areca nuts is the biggest risk factor. Its significant morbidity and high rate of malignant transformation have prompted ongoing efforts to create an efficient management system. In spite of this, prognosis has not significantly improved in decades. This update of the literature offers a critique of managerial flaws as well as diagnostic and treatment problems common in developing nations. In order to prevent these problems and to lessen these shortcomings, an inter-professional model is suggested.

Introduction:

Oral submucous fibrosis (OSMF) is an oral precancerous condition characterized by inflammation and progressive fibrosis of the submucosal tissues resulting in marked rigidity and trismus. OSMF still remains a dilemma to clinicians due to elusive pathogenesis and less well-defined classification systems. According to Pindborg and Sirsat (1966), OSMF is an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although it is sometimes preceded by and/or associated with vesicle formation, it is always associated with a juxtaepithelial inflammatory reaction followed by fibroelastic changes of the lamina propria, with epithelial atrophy causing stiffness of the oral mucosa and trismus, as well as an inability to eat. [1,2]

OSMF is a high-risk precancerous syndrome that has affected millions of people, primarily Indians, and is expected to reach an alarming rate in the near future. Its prevalence rate ranges from 0.2 to 0.5 percent, with a larger percentage observed in southern states. The OSMF malignant transformation rate varies between 5 and 10%. [3] Unlike other precancerous lesions, OSMF is of insidious origin and does not retreat spontaneously or in response to cessation of behaviors. Depending on the severity of the illness, the individual may remain physically and psychologically impaired. The majority of affected persons are young adults and typically exhibit pain, a burning sensation when consuming hot and spicy foods, and a growing inability to open the mouth, resulting in difficulties with mastication and communication. [4]

Table I. Various nomenclatures for Oral Submucous Fibrosis (OSMF)

Years	Details
600	Shushrutha, an ancient Indian Physician, was the chief practitioner of ancient medicine,

Years	Details
B.C.	described a oro -pharyngeal condition called '*Vidari*' in his book 'Shushrutha Samhita', which mimicked to Oral Submucous Fibrosis. Shushrutha Samhita is the ancient treatise which addresses all aspects of general medicine and is considered a foundational text of Ayurveda.
1952	J. Schwartz first described the similar condition in five Indian migrant women, in East Africa- Kenya, under the term *Atropica idiopathica (tropica) Mucosae Oris.*
1953	S. G. Joshi from Bombay – India, broadly described the condition and termed it as *Submucous Fibrosis of palate and pillars.*
1953	D Lal described the pathology as *Diffuse oral submucous fibrosis*.
1954	Su I. P. from Taiwan described similar condition, which he called it as *Idiopathic Scleroderma of mouth.*
1957	J. V. Desa termed the condition as *Submucous fibrosis of palate and cheek.*
1958	A. T. George described the condition as *Submucous fibrosis of palate and mucosa membrane.*
1962	A. B. N. Rao termed the condition as *Idiopathic palatal fibrosis.*
1962	P. N. Behl described the condition as *Sclerosing Stomatitis.*
1962	S. M. Sirsat and V. R. Khanolkar designated the condition as *Submucous fibrosis of the palate.*
1964	Jens J. Pindborg and Satyavati M. Sirsat described the condition as *Juxta epithelial fibrosis.*
1965	Jens J. Pindborg and J. Zachariah emphasized the precancerous nature of OSMF.
1966	Jens. J. Pindborg and Satyavati. M. Sirsat termed the condition as *Oral Submucous Fibrosis* and put forth the definition of OSMF.
1970	Goleria described the condition as *Sub-epithelial fibrosis.*
1970	B. M. Abrol and S. Krishnamoorthy labelled the condition as *Idiopathic Fibrosis.*
1975	K. Ramanathan and S. K. Dharmalingam described OSMF as an *oral precancerous condition.*
1981	K. Ramanathan described the condition as *Asian Sideropenic Dysphagia.*
2005	S. Warnakulasuriya, Newell. W. Johnson, I. Van der Waal Categorized Oral Submucous Fibrosis as *Oral Potentially Malignant Disorder.*
2009	Pankaj Chaturvedi proposed a new name to OSMF as *Gutkha syndrome or Areca nut chewer's syndrome.*
2018	Chandramani More broadly described Oral Submucous Fibrosis as *Areca nut induced Oral Fibrosis and a Collagen metabolic disorder.*
2019	Chandramani More and Naman Rao, Proposed *Clinical Definition for Oral Submucous Fibrosis.*

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CLASSIFICATION OF OSMF

Classification of oral submucous fibrosis

Classification Based on Clinical and Histologic Features

Classification Based on Clinical Features

JV Desa (1957) divided OSMF into three stages as follows: [5]

STAGE 1: Stomatitis and vesiculation

STAGE 2: Fibrosis

STAGE 3: As its sequelae.

Pindborg JJ (1989) divided OSMF into three stage:[6]

Stage 1: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentationand mucosal petechiae.

Stage 2: Fibrosis occurs in healing vesicles and ulcers, which is the hallmark of this stage.

Stage 3: Sequelae of OSMF are as follows:

Leukoplakia is found in more than 25% of individuals with OSMF. Speech and hearing deficits may occurbecause of involvement of the tongue and the Eustachian tube.

Sk Katharia et al (1992) have given different scores assigned to the patients on the basis of mouth openingbetween upper and lower central incisors as follows:[7]

Score 0: Mouth opening is 41 mm or more.Score 1: Mouth opening is 37 to 40 mm.

Score 2: Mouth opening is 33 to 36 mm.

Score 3: Mouth opening is 29 to 32 mm.

Score 4: Mouth opening is 25 to 28 mm.

Score 5: Mouth opening is 21 to 24 mm.

Score 6: Mouth opening is 17 to 20 mm.

Score 7: Mouth opening is 13 to 16 mm.

Score 8: Mouth opening is 09 to 12 mm.

Score 9: Mouth opening is 05 to 08 mm

Score 10: Mouth opening is 0 to 04 mm.

Classifications Based on Histopathological Features of OSMF:

Pindborg JJ and Sirsat SM (1966)[5] were the first to divide OSMF depending only on histopathological features alone are as follows

- **Very early stage:** Finely fibrillar collagen dispersed with marked edema. Plump young fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorphonuclear leukocytes with occasional eosinophils are found.
- **Early stage:** Juxta-epithelial area shows early hyalinization. Collagen still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils and occasional plasma cells.
- **Moderately advanced stage:** Collagen is moderately hyalinized. Thickened collagen bundles are separated by slight residual edema. Fibroblastic response is less marked. Bloodvessels are either normal or compressed. Inflammatory exudate consists of lymphocytes and plasma cells.
- **Advanced stage:** Collagen is completely hyalinized. A smooth sheet with no separate bundles of

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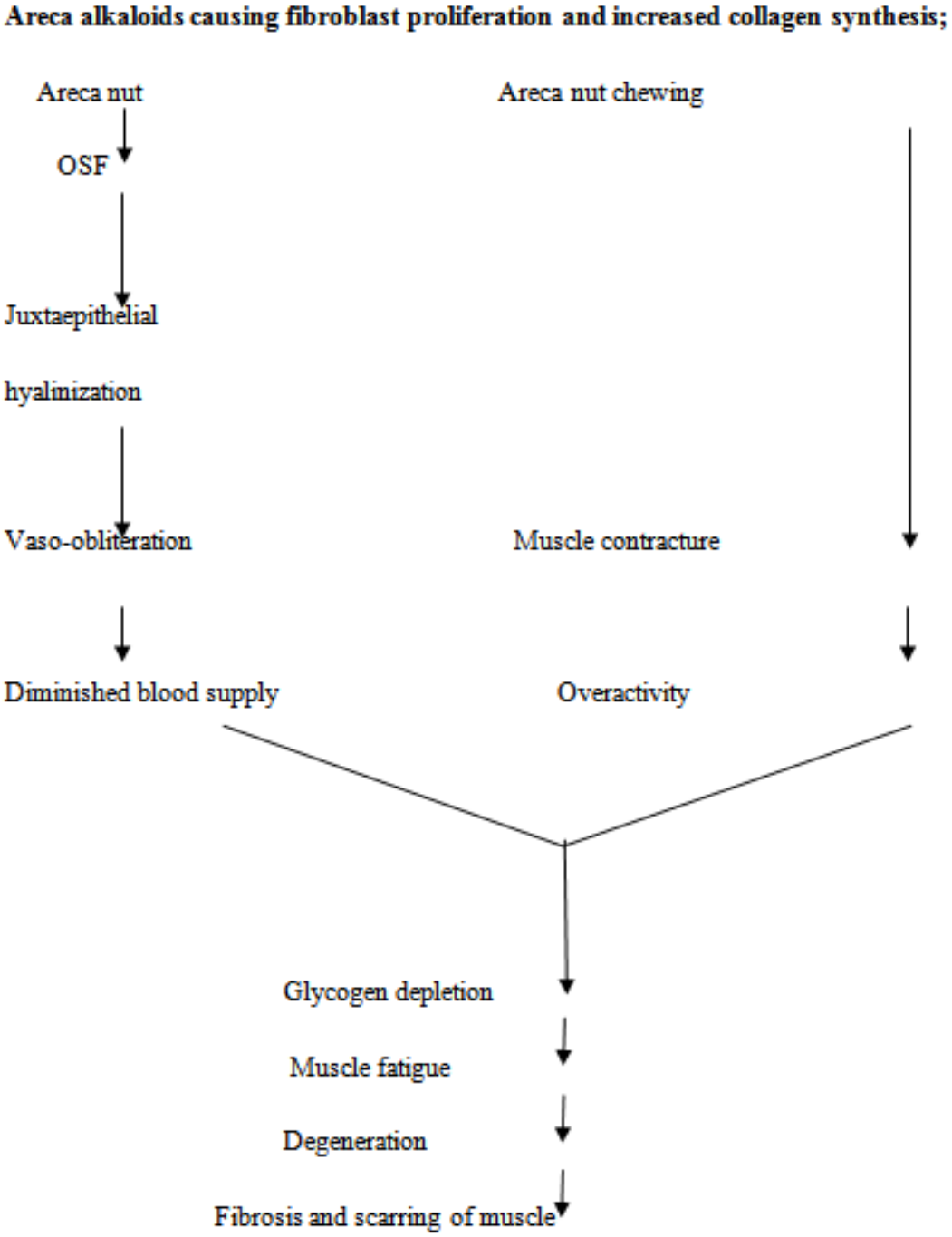
collagen is seen. Edema is absent. Hyalinized area is devoid of fibroblasts. Blood vessels are completely obliterated or narrowed. Inflammatory cells are lymphocytes and plasma cells.

ETIOPATHOGENESIS
ARECA NUT



Role of areca nut in pathogenesis of OSMF (muscle degeneration) (J. N. Khanna 1995).[8]

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CLINICAL FEATURES

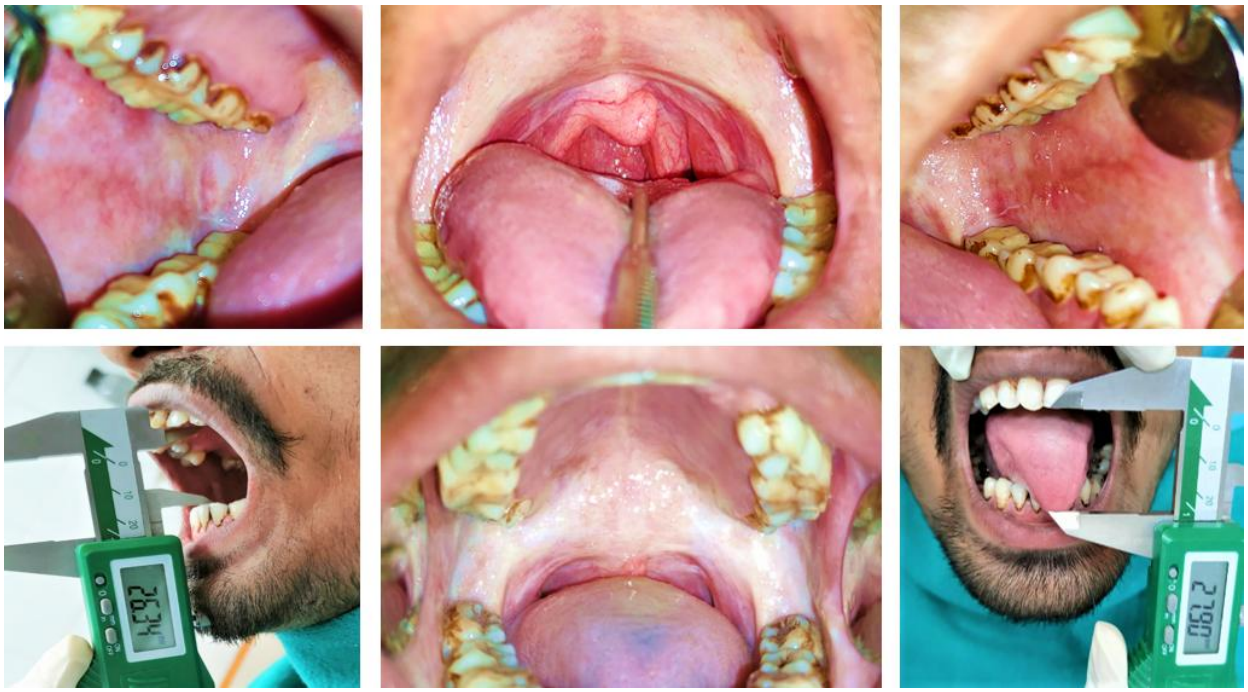

Figure 1. clinical features of OSMF

Oral submucous fibrosis typically affects the buccal mucosa, lips, retromolar areas and the soft palate. Occasional involvement of the pharynx and esophagus is seen. Early lesions present as a blanching of the mucosa imparting a mottled, marble like appearance. Later lesions demonstrate palpable fibrous bands running vertically in the buccal mucosa and in a circular fashion around the mouth opening or lips. As the disease progresses the mucosa becomes stiff, causing difficulty in eating and considerably restricting the patient's ability to open the mouth (trismus). [1]
The classification/grading of OSMF is done according to the degree of trismus, which directly correlates with thedegree of fibrosis, progression of the disease, and location of the lesion in the oral mucosa **(Pindborg 1966).**[5] **Wahi et al (1966)**

Grade I-No symptom referable to mucosal involvement, affects one or more commonly involved anatomic site, focal in character, shows pallor or whitish coloration, wrinkling of mucosa and minimal induration.
Grade II- Symptoms of Soreness of mucosa or increased sensitivity to chillies. The lesion is diffuse, whitish,extensively; indurate involving on one or more anatomical sites
Grade III- Symptoms due to restricted mouth opening, stretching of angles of mouth, inability to protrude thetongue, presence of altered pronunciation and palpable firm submucosal bands.

HISTOPATHOLOGY

Structural changes in oral submucous fibrosis have been studied in detail both at the light and electron microscopic levels. **Van Wyk et al. (1990)** studied the patterns of distribution of different types of collagen in subjects with confirmed oral submucous fibrosis. Ultrastructural findings of muscle degeneration in oral submucous fibrosis were reported by **Cannif (1985).**[9]

Epithelial changes

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Histological findings in OSMF cases were found to vary depending on the clinical severity of the cases and the site of biopsy. The observed epithelial changes are secondary to changes in connective tissue. The findings range from normal to atrophic and hyperplastic epithelium **Pindborg and Sirsat (1966)**[5]observed marked changes in the form of atrophy of epithelium with loss of rete pegs in 90% of the cases as compared to normal oral mucosa.

Connective tissue changes

Characteristically the changes begin in connective tissue and vary with different stages of OSMF. **Pindborg et al (1966)**[5] have described consecutive stages in submucous fibrosis cases based on sections stainedwith haemotoxylin and eosin

The changes are based on following criteria

1. Presence or absence of oedema
2. Nature of the collagen bundles
3. Overall fibroblastic response
4. State of the blood vessels
5. Predominant cell type in the inflammatory exudates.[10]

Very early stage

In this stage, fine fibrillar collagen dispersed with marked oedema, with strong fibroblastic response showing plump young fibroblasts containing abundant cytoplasm will be observed. The blood vessels are occasionally normal, but more often they are dilated and congested. Inflammatory cells, mainly polymorphonuclear leukocytes with occasional eosinophils, are present.

Early stage

In this stage juxta-epithelial area shows early hyalinisation. The collagen is still seen asseparate bundles which are thickened. Plump young fibroblasts are present in moderate numbers. The blood vessels are often dilated and congested. The inflammatory cells are mostly lymphocytes, eosinophils and the occasional plasma cells.

Moderately advanced stage

In this stage, the collagen is moderately hyalinised. The amorphous change starts from the juxta-epithelial basement membrane occasionally, thickened collagen bundles are still seen separated by slight residual oedema. The adult fibroblastic cells have elongated spindle shaped nuclei and scanty cytoplasm. Blood vessels are- either normal or constricted as a result of increased surrounding tissue. The inflammatory exudate consists of lymphocytes, plasma cells and occasional eosinophils.

Advanced stage

Here, the collagen is completely hyalinised and is seen as a smooth sheet with no distinct bundles or oedema. The hyalinised connective tissue becomes hypocellular with thin elongated cells with vestigial nucleus at rare intervals along the bundles. Blood vessels are completely obliterated or narrowed. The inflammatory exudate consists of lymphocytes and plasma cells and occasional eosinophils, Interestingly the melanin- containing cells in the lamina propria are surrounded by dense collagen, which explains the clinically observed loss of pigmentation,

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Lamina propria

The collagen in oral submucous fibrosis are reported as normally banded (sirsat & khanolkar 1987). Several histological and electron-microscopic studies reported that the collagen itself is abnormal. It shows hyaline degeneration, fragmentation, elastic degeneration (Sirsat & Pindborg 1967) and changed staining properties. The ultrastructural features were described as abnormal collagen fibrils, fragmented and bent at odd angles .

Adjacent to the basement membrane there was a thin zone relatively sparsely populated with individual collagen fibrils and loosely arranged groups of fibrils running parallel to the epithelial-connective tissue junction. Some fibrils lacked the typical periodicity of collagen and a similar pattern was seen in submucosa next to salivary glands and muscle bundles.[11]

Diagnosis:

Solid Biopsy

Tissue staining is the most common method of obtaining histological images from solid biopsies. Biomarkers are detected by methylated PCR, real-time PCR, western blotting, and staining techniques. These are used to identify promoter methylation, gene and protein expression levels, and marker locations in the tissues.

Hematoxylin and Eosin (H&E) Stain and Specific Stains

H&E staining is often used as a control for immunohistochemical (IHC) staining as it indicates whether tissue processing has been performed correctly and reveals any artifacts. It clearly elucidates basic tissue morphology by staining the nuclei and cytoplasm purple and pink, respectively. Pathologists make diagnoses based on H&E staining as well as other specific stains and IHC detection in particular cases.

Coding Gene and Protein Biomarkers in OSMF Tissues

Several pathways and molecules associated with hypoxia, the cell cycle, angiogenesis, and EMT are involved in OSMF pathology. Most OSMF cases presented with positive PCNA expression in the basal and suprabasal layers. Proteomic two-dimensional electrophoresis (2-DE) identified cyclophilin A (CYPA) as a biomarker and gene intervention target of OSF. CYPA participates in carcinogenesis. It may promote cell proliferation and inhibit apoptosis by caspase deactivation.

Arecoline induces HIF-1α protein expression in a dose-dependent manner. HIF-1α expression was significantly upregulated in the fibroblasts, epithelial cells, and inflammatory cells of betel quid chewers.

Ki67 and cyclin D1 evaluate cell proliferation while p16 and p53 are tumor-suppressor genes. β-catenin and c-Jun are associated with transcriptional activity. The hepatocyte growth factor receptor c-Met and the insulin-like growth factor II mRNA-binding protein 3 (IMP3) are linked with tumor invasion. In OSMF, Ki67, cyclin D1, c-Met, and IMP3 are upregulated but β-catenin is downregulated.

Non-Coding Gene Biomarkers in OSMF Tissues

Certain microRNAs are stable in frozen or paraffin-embedded tissues and low copy numbers may nonetheless be analyzed by reverse-transcription qPCR. The miR-200b and miR-200c were downregulated in OSMF specimens. Arecoline treatment reduced miR-200c expression in buccal mucosal fibroblasts. The miR-200c and miR-200b upregulated E-cadherin by targeting ZEB1 and ZEB2, respectively. ZEB1 binds to the α-smooth muscle actin (α-SMA) promoter and induces α-

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SMA which is overexpressed in the myofibroblasts during fibrogenesis.

Liquid Biopsy

Current biochemical and biomolecular techniques are more stable and sensitive than their predecessors. Even low concentrations of free ions, circulating cells, proteins, nucleic acids, and enzymes may be detected in body fluids. Serum protein and globulin levels were significantly decreased in OSF relative to normal tissues. Serum copper levels gradually increased as OSMF transformed into OSCC along with the duration of the betel quid chewing habit. In recent years, OSMF biomarkers have been identified in serum and saliva and the feasibility of their application in OSF diagnosis has improved as evidence and sample sizes have increased.

Biomarkers in OSMF Serum

The rates of sister chromatid exchange per lymphocyte in patients with OSF and pan chewers were significantly higher than those in healthy controls. ROS-induced DNA damage is responsible for genome instability. The levels of the provitamin A carotenoid β-carotene decreased with OSMF progression. Erythrocyte superoxide dismutase (E-SOD) and glutathione peroxidase (GPx) levels were significantly lower in the OSF, oral leukoplakia, and oral cancer groups than in the control. Lactate dehydrogenase (LDH) catalyzes the oxidation of lactate to pyruvate and its levels are markedly elevated in several potentially malignant lesions/conditions and oral cancer. Serum LDH levels were directly correlated with betel chewing frequency and mouth opening in OSF patients. On the other hand, no such associations were found for salivary LDH. Serum LDH may be a better biological marker of OSMF than salivary LDH. OSMF patients presented with elevated DNA damage and lipid peroxidation levels compared with healthy controls. As malondialdehyde (MDA) is a lipid peroxidation marker, the evaluation of its levels by comet assay may help identify OSF patients with high malignant potential.

MANAGEMENT OF OSMF

Table II. Summary of the conservative therapy of OSF and the molecular targets of each therapy.

Physical Therapy	**Molecular Targets**
Hyperbaric oxygen treatment (HBO)	Promote the apoptosis of fibroblast, and inhibit TNF-α, TGF-β, and the activation of collagen synthesis.
Drug therapy	**Molecular Targets**
Dexamethasone	Anti-inflammation (block the action of inflammatory mediators)
Methylprednisolone	Anti-inflammation (block the action of inflammatory mediators)
Betamethasone	Anti-inflammation (block the action of inflammatory mediators)
Hyaluronidase	Hydrolyze the hyaluronan
Chymotrypsin	Hydrolyze the collagen
Pentoxifylline	Anti-inflammation.

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	Inhibits TNF-α and leukotriene synthesis
Colchicine	Anti-inflammation, neutralized cytokines (TGF-β, IL4, IL6) Increase collagenolytic activity
Natural compounds remedies	**Molecular Targets**
Butylidenephthalide	Decrease α-SMA and fibronectin and type 1 collagen A1 expression Inhibit myofibroblast activity (migration and contraction)
Glabridin	Decrease α-SMA, type I collagen, and TGF-β Inhibit myofibroblast activity (migration and contraction)
Asiatic acid	Inhibit TGF-β1, collagen 1 type 2, and collagen 3 type 1
Tanshinone	reactivate p53
Salvianolic acid B with Triamcinolone acetonide	Inhibit the transcription of procollagen gene COL1A1 and COL3A1 Decrease TIMP-1/-2 expression Inhibit the transcription and release of CTGF, TGF-β1, IL-6 and TNF-α Increase MMP-2/-9 activity
EGCG	Inhibit TGF-β1 to suppress early growth response-1 (Egr-1) Suppress the cellular ROS Inhibit the CTGF and TGM-2 expression
Aloe Vera	Anti-inflammation Reduce inflammasome formation
Curcumin	Inhibit p53, TGF-β, and iNOS Reduce CTGF
Lycopene	Antioxidants
Honey	Anti-inflammation, anti-oxidation Inhibit lipoxygenase, IL-1, IL-10, COX-2 Scavenge free radicals Inhibit NF-κB signaling pathway

Restriction of Habit behavioral therapy

Reduction or even elimination of the habit of areca nut chewing is an important preventive measure. At least in the early stages of OSMF, it could probablyslow the progress of the disease

(a) Nutritional support- Supplementary diets administered to OSMF patients

are mainly for high protein and calories and for vitamin B complex and other vitamins and minerals. These are commonly employed in combination with other more specific therapeutic agents like ingestion of iodinated salt and/or local applications .[11]

Use of Steroids Local injections of dexamethasone, hyaluronidase and placental extract have been tried. In vitro, collagen from patients with OSMF, in contrast to normal collagen, is attacked rapidly by hyaluronidase.

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Corticosteroids:

OSMF is always associated with juxta-epithelial inflammatory response. The use of corticosteroids suppresses inflammatory response by their anti-inflammatory action. It prevents fibrosis by decreasing fibroblastic proliferation and deposition of collagen. Corticosteroids can be administered as local injection (intralesional injection), topical applications or in the form of mouth washes. Widely used preparations are dexamethasone, 4 mg biweekly injection, for a period of 10 weeks. (Betnesol) 0.5 mg mouthwash is given to relieve pain and burning sensation, for topical application triamcinolone 0.1% is given for 37 relief of pain and burning sensation.[11]

Hyaluronidase:

Experimental studies revealed that collagen altered in vivo is susceptible to fibrinolytic enzymes such as hyaluronidase, trypsin and elastase (Satyavathi, Sirsat). Hyaluronidase is known to break down hyaluronic acid, lower the viscosity of the intercellular cement substance and also decreases collagen formation. Intralesional injection of Hyalase (Rallis India) used in the dose of 1500 IU, Chymotrypsin (Waltor Bushnell India) 5000 IU. Fibrinolytic agents (Hyalase) were found to be acceptable by patients.[11]

Placental Extracts (placentrex)

Such extracts, in the form of the local injections, have been tried with varied results. The combination of dexamethasone, hyaluronidase and placental extract were found to give better 62 results than with a single drug.[11]

Surgical Technique

Surgical Treatment : Excision of fibrotic tissues and covering the defect with split thickness skin, fresh human amnion or buccal fat pad (BFP) grafts have been applied to treat OSMF.[11]

SUPPORTIVE THERAPY

Along with medicinal and surgical management supportive measures should be used like

1. Physiotherapy
2. Microwave diathermy
3 Oral stents [11]

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