



## Current Management Strategies in Oral Submucous Fibrosis

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**Abstract:** Oral sub-mucous fibrosis is a premalignant condition recently recognized as "areca nut-induced oral fibrosis." It is "a chronic disease which is irreversible, affecting oral and systemic health of patients." However, Areca nut or betel nut is the primary etiologic reason for Oral Submucous fibrosis (OSMF); other factors like excess chilies intake, nutritional deficiencies, and immunological factors are also considered causative agents for the disease. It causes inflammation and fibrosis of the submucosal tissues causing trismus and rigid oral mucosa. The treatment for this disorder includes numerous conservative, medicinal, and surgical management; however, no treatment modality has been proven to be a standard treatment option. Herbal modalities are seen to be more effective in OSMF treatment. Unfortunately, the literature on the management of OSMF cannot do justice to all the treatment modalities at one stop. The new trends and treatment modalities for OSMF keep adding up from time to time, and yet formulating the perfect treatment protocol for OSMF management is still challenging for dental clinicians due to the multifactorial etiology, complexity of the disease, and changing trends in treatment. The present review aimed to enlighten clinicians about the current disease scenario and tried to include all the latest treatment modalities. The objectives are to review and assess the existing situation of this disease with a brief on the efficacy of different available treatment modalities used to help dental physicians formulate a treatment protocol with knowing the proper effects, advantages, and disadvantages of each modality and enlightening the potential future treatment options for OSMF.

**Keywords:** OSMF, Atrophica Idiopathica, Fibrous bands, Aloe Vera, spirulina, Pentoxifylline, Chymotrypsin.

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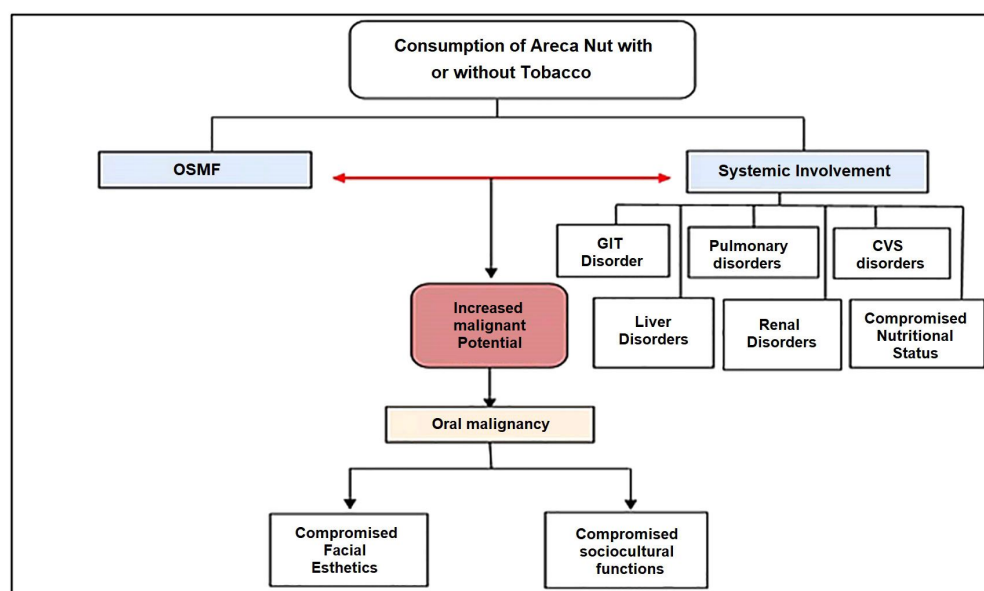
## I. INTRODUCTION

As the name suggests, oral submucous fibrosis (OSMF) is "an irreversible, debilitating chronic state of oral mucosa: in which formation of fibrous tissue is a characteristic feature<sup>1</sup> Dr. S. G. Joshi, in 1953, is considered the first to coin the term OSMF, later J. J. Pindborg defined it in 1965, and the latest clinical definition given by More and Rao as " a debilitating, progressive, irreversible collagen metabolic disorder induced by chronic chewing of areca nut and its commercial preparations; affecting the oral mucosa and occasionally the pharynx and esophagus; leading to mucosal stiffness and functional morbidity; and has a potential risk of malignant transformation."<sup>2-3</sup> Betel nut and betel nut product consumption are considered the primary causative factors leading to the formation of fibrous bands in the oral mucosa.<sup>4,5</sup> OSMF is commonly found in South Asian countries India, Pakistan, Bangladesh, and Sri Lanka<sup>4,6</sup> Several management modalities have been proposed since the last 65 years when Schwartz coined the term in literature in 1952. About its high rate of malignant transformation, for prevention of this

debilitating disease and habit-related oral cancer, there is a necessity for Oral medicine professionals and dentist–scientists from around the world.<sup>7,8</sup> The majority of the affected population belongs to the older age group.<sup>8</sup> However, an increasing incidence in children and adolescents, as published in the recent study literature.<sup>9</sup> The primary objective of this article is to brief the existing situation of this disease to discuss the current management strategies for this disorder.

## 2. ETIOPATHOGENESIS

Numerous theories have been put forth explaining the etiopathogenesis of this oral premalignant disorder. The chief etiological factor is the areca nut, a dried seed endosperm. Rural people primarily use Areca or betel nut because it aids digestion and stimulates the central nervous system. It is considered Group I carcinogen. Although Areca nut and tobacco cause OSMF also, the effects are systemic. It affects gastrointestinal disorders, liver disorders, pulmonary disorders, nutritional deficiencies, and cardiovascular and renal disorders (Figure 1).



**Fig 1: Possible diseases pattern in Areca nut habitual patients**

**Abbreviations:** GIT- gastrointestinal, CVS- cardiovascular

Areca nut primarily contains alkaloids which are arecaidine, arecoline, guvacoine and guvacine, and flavonoids like catechins, tannins, and copper, all of which have roles in the OSMF pathogenesis.<sup>10</sup> The alkaloids act by stimulating the proliferation of fibroblasts, causing an increase in collagen formation. While flavonoids increase lysyl oxidase (LOX) activity, an enzyme that causes an increase in collagen cross-linking, thus making proteolysis-resistant collagen.<sup>11</sup> Copper is found in areca nut in high amounts; it enhances the LOX enzyme, upregulating the progression of this disease. Nutritional deficiencies (iron, zinc, essential vitamins), genetic predisposition (increased frequency of DR3 and DR7 and human leukocyte antigen 10 in OSMF), and molecular mechanisms (growth factors and cytokines) are other potential supplemental etiological factors.<sup>8</sup>

### 2.1. Clinical Signs, Symptoms, and Diagnosis

OSMF is prevalent in the middle-aged group, the highest in the 20 to 40. The prevalence is six times more in males than

females; however, the gender preference varies geographically.<sup>10</sup> Buccal and labial mucosa, soft and hard palate, retromolar area, the floor of the mouth, faucial pillars, lips, tongue, and gingiva are commonly affected sites. The patients usually report reduced mouth opening and burning oral sensation while consuming spicy food. Blanching of the mucosa, vesicle formations, diffuse melanosis, and petechiae are the signs in the initial stages of the disease.<sup>10,12</sup> In some advanced cases, submucosal tissue rigidity gives the mucosa a white marble-like mottled appearance.<sup>11</sup> Atrophy of the uvula causes altered shape, a very common finding.<sup>11</sup> Due to the fibrosis tongue sometimes becomes rigid and de-populated, along with altered taste sensation and defective speech. The extra oral features include a sunken cheek appearance with prominent malar bones, thinning of lips, loss of nasolabial fold, increased philtrum area and ellipsoid, and limited mouth opening. In some advanced cases, there can be Stenosis of the Eustachian tube causing hearing impairment. With less than 5mm interincisal mouth opening, it is considered severe OSMF and can lead to fibrous Temporomandibular joint (TMJ)

ankylosis. OSMF is diagnosed primarily based on the clinical signs and symptoms described above.<sup>10</sup>

### 3. MANAGEMENT STRATEGIES

Numerous researchers have enlightened and worked on the pre-existing etiopathogenesis of OSMF. Restricted mouth opening, burning mucosa while having food, and altered speech are a few of the main symptoms of SMF. The stage and severity of clinical involvement are extremely important in formulating the treatment plan. In the initial stages, non-surgical treatment is considered, while for severe stages, surgical management is an option of choice.

#### I. CONSERVATIVE MANAGEMENT

Conventional treatment modalities include complete stoppage of habits, oral physiotherapy, and nutritional or supportive therapy.

##### a) Discontinuation of habits

Patient counseling, motivation, and education for habit cessation in the early stages of OSMF is a crucial step in management, as it will slow down the disorder's progression rate.<sup>13</sup>

##### b) Physical therapy

Physiotherapy is intended to increase the mouth opening by putting pressure on the fibrous bands using mouth opening exercises with the help of ice cream stick exercises and various out splints, lateral and extended movements of the tongue, which is supposed to put stress on fibrous bands, can be helpful to avoid more restricted mouth opening.<sup>13</sup>

##### c) Microwave diathermy

Microwave diathermy causes juxta-epithelial connective tissue heating very selectively and is hence restricted to the area of interest. Heat therapy causes fibrinolysis of bands. It's easy to use with minimal discomfort to the patient.<sup>14</sup>

#### II. MEDICINAL MANAGEMENT

Treatment consists of intra-lesional injections of steroids, fibrinolytic agents, and placentrex. Medicinal treatment is intended to improve symptoms and increase movements.

##### A. Local Drug Delivery

*Hyaluronidase* degranulates excess collagen in OSMF, not the normal collagen; it has been proven in many in-vitro studies. In their study,<sup>11-13</sup> Kakar et al. used 1500 I.U of hyalase dissolved in 1cc of 2% lignocaine, when given locally for 7 weeks, showed better outcomes when followed by Hyaluronidase injections next 3 weeks.<sup>14</sup> Injecting collagenase into the mouths of 18 OSMF patients led Kumar K to the two findings: there was the maximum improvement in the color of the mucosa, reduced burning sensation, and increased mouth opening from 3 mm to 10 mm; however, he also noticed variable adverse effects, including pain, swelling, and trismus after each collagenase injection.<sup>15</sup> *Chymotrypsin* is an "endopeptidase enzyme" which can carry out proteolysis, which causes the breakdown of tissue fibrosis.<sup>16</sup> Its proteolytic

and anti-inflammatory action is useful in the treatment of OSMF.<sup>16</sup>

##### B. Immunomodulatory Drugs

*Corticosteroids* are immunosuppressive drugs reducing inflammation in OSMF, hence controlling this disorder. Furthermore, steroids are supposed to reduce fibroblast proliferation, decreasing collagen deposition.<sup>13</sup> Topical application of steroids in patients or Sub-mucosal intra-lesion injections weekly with moderate OSMF may aid in reducing further damage. Topical steroid ointment application may be helpful in painful oral ulcers. Results for hydrocortisone injection 1.5 cc, when delivered locally, were effective.<sup>13</sup> *Colchicine* is an alkaloid found in the crocus-like plant, *Colchicum Autumnale*, with anti-fibrotic and anti-inflammatory properties that reduce the burning sensation for OSMF.<sup>16</sup> *Immune milk* is proven to have anti-inflammatory properties and contains multiple vitamins, nicotinic and folic acid, pantothenic acid, iron, zinc, and copper. IgG antibodies are also present in immunized milk that have an anti-inflammatory action and modify cytokine collection, which is important for noticeable development in OSMF patients.<sup>13</sup> *IFN-gamma* has an immunoregulatory effect and plays a very important role in OSMF treatment. Haque et al., in their study, found that anti-fibrotic cytokine IFN-gamma cause a direct effect on collagen production. This study of IFN gamma local injections showed significant enhancement in mouth movements.<sup>17</sup>

##### C. Antioxidants, micronutrients, and Other Drugs

An effective antioxidant called "lycopene" is present in tomatoes, which is also anticarcinogenic and has gained popularity due to noteworthy benefits in premalignant lesions like leukoplakia.<sup>13</sup> It has a singlet-oxygen-quenching ability 10 times higher than alpha-tocopherol and twice as high as beta-carotene. It has an anti-inflammatory action and also, increases lymphocyte stress resistance, and inhibits fibrogenesis.<sup>17,18</sup> *The polyphenols in green tea* have scavenging activity against free radicals and can protect DNA in cells, usually due to free reactive oxygen radicals. It decreases the proliferation of tumor cell rate and carries out apoptosis of senescent cells. Henceforth, a number of the potential benefits of tea besides its antioxidant property.<sup>13</sup> *Aloe vera* is famous for its antimicrobial, anti-inflammatory, and remedial properties. A primary report for differentiating the adequacy of aloe vera with cell reinforcements in OSMF management was carried out in a study by Sudarshan et al.<sup>18</sup> The consequences of the review were that aloe vera reaction is improved in every one of the boundaries assessed and reacted in the clinical - histopathological arrangements predominantly in early clinical and histopathological stages.<sup>18</sup> *Aloe vera* use also improves the burning sensation of the oral mucosa, cheek flexibility, and mouth opening. It was believed that aloe vera causes a decrease in the burning of oral mucosal and improves mouth movements, upgrading patient satisfaction.<sup>18</sup> *Curcumin* (diferuloylmethane), a natural yellow color pigment found in turmeric, contains anti-inflammatory, antioxidant, and anticarcinogenic properties. Turmeric oleoresin and oil together protect against DNA harm. Accordingly, curcumin act as an anti-inflammatory and anticarcinogenic agent. It likewise gives a base to a simple, safe, cost-effective, and acceptable interference for mild phases of oral submucous fibrosis. Curcumin regulates the inflammatory reaction by decreasing enzymes like lipoxxygenase, cyclooxygenase-2 (COX-2), and nitric oxide synthase (iNOS).<sup>19</sup> It represses the

formation of the provocative cytokines, monocyte chemoattractant protein (MCP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Interleukin -1, 2, 6, 8, 12, and movement inhibitory protein. Rai et al., in their study, used curcumin for treating oral precancerous lesions. The study included 25 OSMF, and a noticeable reduction in symptoms was recorded in curcumin patients. Also, there was an increment in the vicinity and systemic cell reinforcement status.<sup>11,19</sup> *Spirulina* alga is the source of multiple vitamins, minerals, phycocyanin, and carotenoids. It became popular because of its ability to decrease cholesterol levels.<sup>11</sup> The antioxidant properties have been studied in some recent studies.<sup>11,13</sup> It causes a rise in IL-2 and inhibits IL-6, exhibiting its antioxidant property. It has chemo-preventive properties because it contains abundant superoxide dismutase and beta carotene, subsequently aiding in treating oral premalignant lesions.<sup>13</sup> *Oxitard* is the extracts of '*Mangifera indica*, *Withania somnifera*, *Daucus carota*, *Glycyrrhizaglabra*, *Emblca officinalis*, *Vitis vinifera*, *Triticum sativum*, *Yashada bhasma*,' an ayurvedic agent with antioxidant properties.<sup>12</sup> Antibiotic and antiviral action of '*Mangifera indica*. '*Withania somnifera*' is responsible for enhancing overall health and well-being as it is antianxiety, anti-inflammatory, and reduces stress. '*Daucus carota*' contain a profound amount of vitamin A. '*Glycyrrhiza glabra*' has immunostimulatory action that reduces inflammation and regularizes the vocabulary function. '*Vitis vinifera*' is scathing and anti-inflammatory, thereby decreasing the burning of the oral mucosa. '*Emblca officinalis*,' also known as Indian gooseberry, is a potent source of Vit C, and '*Yashada bhasma*' has zinc, promoting cell regeneration and wound healing. And minerals in '*Triticum sativum*' lower oxidative stress.<sup>12,13</sup>

### 5.1. Salvianolic acid

The dried root of a herb called '*Salviamiltiorrhizabage*.' *Radix Salvia emiltiorrhizae* (danshen)" is a well-known product among the native population of China. Seven phenolic hydroxyls in Salvianolic acid B (Sal-B) have immense antioxidant activity. Also, it is a potent ingredient in Danshen.<sup>13</sup>

## III. SURGICAL MANAGEMENT

The last treatment of option is surgery for severe cases like patients with minimal mouth opening and in patients showing dysplastic or neoplastic changes in the biopsy.<sup>20</sup> Surgery option includes:

### a. Fibrotomy

It involves fibrous band cutting followed by the forced opening of the jaw. It is not practiced nowadays due to its higher frequency of relapse of trismus post-surgery.<sup>18</sup>

### b. Fibrotomy with grafts

Inter-positional graft materials are used to prevent scar formation, which eventually causes relapse of trismus due to just surgical elimination of fibrous bands.<sup>20</sup>

### c. Extra-oral flaps

Various extra oral flaps are carried out like

1. Nasolabial flap.
2. Split thickness skin graft.
3. Platysma myocutaneous muscle flap.

4. Superficial temporal fascia pedicled flap.

### d. Intraoral flaps

The intraoral flaps like the Tongue flap, Buccal fat pad, Palatal-island flap, Microvascular free flaps like the Anterolateral thigh flap, Radial forearm free flap, Alloplastic flaps (Collagen membrane) give the advantages of no extraoral scars and are not aesthetically compromising.<sup>20</sup>

### e. Laser treatment

The laser with 2780 nm wavelength erbium chromium yttrium scandium gallium garnet (Er Cr: YSGG) is most commonly used. It is well absorbed by water and does not create thermal damage on oral soft tissue. An almost bloodless operative field is the main advantage of laser surgery and thus requires less local anesthetic, provides brilliant visibility, minimizes chances of infections, minimal tissue trauma, lesser sutures, reduced healing time, and limited post-operative edema.<sup>21</sup> Chaudhary et al. conducted a study by treating moderate cases of bilateral OSMF using Er Cr: YSGG laser, and during follow-up, it showed better results.<sup>22</sup>

## IV. STEM CELL THERAPY

In a study on stem cell therapy effectiveness in the OSMF treatment by accessing interincisal distance and functioning and with 5-year follow up accessing the sustainability of result.<sup>19</sup> Total seven patients were there. Out of the four were treated with stem cells obtained by the point of care delivery system, and the remaining three were treated using the stem cells of the Ficoll et al. method.<sup>19</sup> Post-treatment clinical symptoms and histo-pathological changes are assessed. The follow-up period of patients varies from 6 months to 5 years. Reduced blanching, increased mucosal flexibility, decreased burning sensation of oral mucosa on having spicy food, and improved interincisal mouth opening were noted. After the follow-up visits, the results were found to be sustained in patients.<sup>21</sup>

## 4. CONCLUSION

This review of literature focuses on recent advancements in treating oral submucous fibrosis. Different treatment options used to treat the disease are corticosteroids, herbal modalities, hyaluronidase injections, placentrix, IFN, microwave diathermy, etc. Mononuclear stem therapy can be the future treatment for OSMF patients with promising results. In addition, recent data have shown that combination therapy personalized for patients according to their nutritional profiles effectively manages this disease. Although more extensive clinical is necessary with more sample size and including multiple parameters before declaring any specific modality to be definitive in the OSMF treatment.

## 5. LIMITATIONS

Although the limitation of the article is that it does not specify how to choose the treatment modality for the specific patient, as OSMF is not only oral but a systemic condition, so every aspect of the patient, like the type of habit, its frequency, the severity of the disease systemic, and genetic predisposition should be evaluated before formulating the treatment protocol.

## 6. AUTHORS CONTRIBUTION STATEMENT

Dr. Simran Badki Gathered the data and prepared the manuscript, Dr. Vidya K. Lohe conceptualized this review, Dr. Rahul Bhowate gave his valuable inputs for improvising the review, Dr. Suwarna Dangore did the final corrections and approved the manuscript, Dr. Mrunal Meshram, and Dr.

Pragati Bhargava gave their inputs for designing the manuscript. Finally, all the authors read and approved the final version of the manuscript.

## 7. CONFLICT OF INTEREST

Conflict of interest declared none.

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