***Review Article***

**An overview on Oral Submucous Fibrosis: Aetiology, Diagnosis, and Advances in Management**

**ABSTRACT**

This comprehensive review examines the intricate facets of OSF, encompassing its etiology, clinical features, diagnostic modalities, management strategies, and preventive measures. Oral Submucous Fibrosis (OSF) represents a multifactorial and potentially malignant condition affecting the oral cavity, with significant implications for public health. Investigating the interactions between areca nut usage and additional risk factors enhances our understanding of OSF’s complexity. Drawing insights from recent research articles, the review highlights the multifaceted nature of OSF, emphasizing the central role of areca nut and betel quid chewing in its pathogenesis. Diagnostic approaches, including clinical examination, histopathological analysis, and adjunctive tools, are explored, underscoring the importance of early detection for effective intervention. Multidimensional management strategies, ranging from behavioural change to surgical options, are discussed, emphasizing the need for tailored approaches based on individual needs. Preventive paradigms, including public health awareness campaigns and regulatory measures, are elucidated, highlighting the importance of community-driven efforts in mitigating OSF’s impact. The conclusion underscores the necessity of ongoing research, collaboration, and community engagement in addressing the complex challenges posed by OSF, ultimately aiming to enhance global oral health outcomes.

Keywords: oral submucous fibrosis, areca nut, mucosal stiffness

**INTRODUCTION**

Oral Submucous Fibrosis (OSF) stands as a complex, potentially malignant condition affecting the oral cavity, characterized by progressive fibrosis of the submucosal tissues. OSF may cause decay in the epithelium, consequently expanding the cancer-causing agent infiltration. Arecoline is a drying up operator and may recoil the cells enough to allow permeation of cancer-causing agents through the epithelium to arrive at the basal layer, which is the separating cell layer where neoplastic cell transformation may happen [23]. As we navigate this exploration, drawing insights from recent research articles, we aim to unravel the challenges posed by OSF and shed light on emerging perspectives that contribute to a deeper understanding of this condition, ultimately paving the way for more effective prevention and management strategies [17-20]. Currently, the treatment of OSF mainly includes physical therapy, hyperbaric oxygen therapy, drug therapy, and surgical treatment. Drug therapy is the most common treatment, and available drug treatments include steroids, exogenous enzymes, multivitamins and micronutrients, peripheral vasodilators, human placental extracts, and other therapeutic agents. Although various treatments have been proposed for OSF over the past few decades, satisfactory results have not been achieved with most methods [21,22]. This comprehensive review explores the multifaceted aspects of OSF, delving into its intricate etiology, clinical manifestations, diagnostic approaches, therapeutic interventions, and the broader implications for public health.

**ETIOLOGY AND RISK FACTORS**

Oral Submucous Fibrosis (OSF) is a chronic, debilitating condition with a multifactorial etiology, often intertwined with cultural practices and regional habits. Understanding the intricate web of factors contributing to OSF is essential for developing targeted prevention and intervention strategies.

ARECA NUT AND BETEL QUID: Primary Culprits in OSF

Central to the genesis of OSF is the habitual consumption of areca nut, frequently chewed in combination with betel leaf, slaked lime, and occasionally tobacco – collectively known as betel quid. The areca nut, a common psychoactive substance in many Asian countries, contains alkaloids such as arecoline, which is implicated in the fibrogenic process underlying OSF. Studies, including the comprehensive work by Maher R et al. (2019), emphasize the direct correlation between areca nut usage and OSF development(1).

ARECOLINE AND FIBROGENIC MECHANISMS:

Arecoline, the primary alkaloid in the areca nut, has been identified as a potent fibrogenic agent. It induces collagen synthesis and alters fibroblast function, leading to increased deposition of extracellular matrix components. The cascade of fibrogenic events triggered by arecoline plays a pivotal role in the pathogenesis of OSF. Insights from molecular studies, such as those conducted by Nair U et al. (2021)(2), shed light on the intricate mechanisms through which arecoline induces fibrosis.

GENETIC PREDISPOSITION AND SUSCEPTIBILITY:

While environmental factors play a significant role, genetic predisposition also contributes to the susceptibility of individuals to OSF. Genetic variations in collagen metabolism, immune response, and detoxification pathways have been studied to understand the differential susceptibility observed among individuals exposed to areca nut. Research studies, including the work by Jayalekshmi PA et al. (2020), delve into the genetic factors influencing OSF susceptibility(3).

NUTRITIONAL DEFICIENCIES:

Deficiencies in iron, vitamins, and essential micronutrients have been implicated as risk factors for OSF. Malnutrition and poor dietary habits exacerbate the fibrotic process, influencing the severity of the condition4.

SYNERGISTIC EFFECT WITH TOBACCO AND ALCOHOL:

The synergistic effect of areca nut chewing with other risk factors, such as tobacco use and alcohol consumption, compounds the severity of OSF. The coexistence of these risk factors increases the risk of malignant transformation. Investigating the interactions between areca nut usage and additional risk factors enhances our understanding of OSF’s complexity. Studies exploring these interactions, including the work by Murti PR et al. (2018)(5) , offer valuable insights into the combined impact of these risk factors.

**PATHOGENESIS**

Oral submucous fibrosis is a collagen metabolism disease. Changes in the extracellular Matrix may occur in this. Alkaloids, flavonoids, and copper found in areca nut disrupt the extracellular matrix’s equilibrium. Four alkaloids are known to induce the production of collagen by fibroblasts: arecaidine, guvacine, guvacoline, and arecoline (the most effective). Collagenase is inhibited by flavonoids (tannins and catechins), which also stabilize the collagen fibrils and make them resistant to collagenase’s breakdown.

When areca-nut or gutkha create localized mucosal inflammation, activated T-cells and macrophages are drawn in, which increases the production of cytokines and tumor growth factor-beta (TGF-beta) triggering procollagen genes, procollagen proteinase enzymes, and lysyl oxidase activity, the latter significantly boosts collagen synthesis. TGF- beta simultaneously prevents the breakdown of collagen by triggering the Plasminogen activator inhibitor (PAI) and the tissue inhibitor of matrix metalloproteinase (TIMP) genes. It has been discovered that the high copper content in areca nuts stimulates the activity of lysyl oxidase, an enzyme necessary for the ultimate cross-linking of collagen fibers.

Chewing acacia continuously causes the masticatory muscles to become more active, glycogen to be depleted, and muscle exhaustion to occur. The decreased blood flow that follows fibrosis. This leads to significant muscle fibrosis and degeneration, as well as increased muscle fatigue(14).

**CLINICAL FEATURES**

Oral Submucous Fibrosis (OSF) manifests through a spectrum of clinical features that progressively affect the oral mucosa. Understanding these manifestations is crucial for timely diagnosis and intervention. In this detailed exploration, we delve into the intricate clinical aspects of OSF, drawing insights from recent research articles.

STAGES

According to Passi D et al. (2017)

Table 1 : **CLINICAL FEATURES OF MOUTH OPENING**

|  |  |  |
| --- | --- | --- |
| **STAGES** | **CLINICAL FEATURES** | **MOUTH OPENING** |
| Grade 1 | 1/3rd oral cavity involved, gentle blanching, presence of burning sensation, shows recurrent ulceration and stomatitis, dryness of mouth. | Up to 35 mm |
| Grade 2 | 1/3rd to 2/3rd oral cavity involved, evidence of blanching in oral mucosa with mottled and marble like appearance, fibrotic bands palpable and involvement of soft palate and premolar area. | 25mm to 35mm  Cheek flexibility reduced by 33% |
| Grade 3 | Greater than 2/3rd oral cavity involved, extreme blanching, presence of broad thick fibrous palpable band at cheek and lips and rigid mucosa, presence of depapillated tongue , shows restricted of tongue , shrunken bud like uvula, floor of the mouth involved, lymphadenopathy. | 15mm to 25 mm  Cheek flexibility reduced by 66% |
| Grade 4 | Evident of Leukoplakia changes, Erythroplakia, ulceration, and suspicious malignant lesion. | Less than 15mm |

10

MUCOSAL STIFFNESS AND REDUCED MOUTH OPENING:

One of the earliest signs of OSF is the development of mucosal stiffness, often accompanied by a gradual reduction in mouth opening. As fibrotic changes ensue, the affected individuals experience difficulty in opening their mouths fully, a phenomenon known as trismus. This initial presentation serves as a diagnostic hallmark6.

FIBROTIC BANDS AND BLANCHED ORAL MUCOSA:

As OSF advances, fibrotic bands form within the oral mucosa, leading to a characteristic blanching or pallor of the affected areas. These fibrous bands often extend across the buccal mucosa, palate, and oropharynx, contributing to a distinct clinical appearance. The work of Rajendran R et al. (2020)(6) provides insights into the clinical staging of OSF, emphasizing the progression of fibrotic changes and their impact on oral tissues.

ALTERED SALIVARY FUNCTION AND DRY MOUTH:

OSF can disrupt salivary gland function, leading to reduced saliva production and, consequently, a persistent sensation of dry mouth. This symptomatology not only affects oral comfort but also contributes to difficulties in speech, mastication, and overall oral hygiene. Research studies, such as those by Murti PR et al. (2018)(5), shed light on the functional consequences of OSF on salivary glands.

EROSIVE CHANGES AND ULCERATION:

The fibrotic changes in OSF may result in erosive lesions and ulceration within the oral cavity. These alterations increase the susceptibility to secondary infections and contribute to patient discomfort. Comprehensive clinical examinations, as discussed in studies like Maher R et al. (2019)(1), highlight the importance of identifying erosive changes for a holistic understanding of OSF’s clinical presentation.

POTENTIALLY MALIGNANT TRANSFORMATION:

OSF is recognized as a potentially malignant disorder, and its prolonged existence significantly elevates the risk of malignant transformation, particularly to oral squamous cell carcinoma. Regular monitoring and timely intervention are essential to identify any signs of dysplasia or malignant changes. Longitudinal studies, including those outlined by Sinor PN et al. (2017)(7) , emphasize the importance of surveillance for malignant transformation in OSF. According to Namon R Roe, Alessandro villa, Chandramani B , a 17-year follow-up study published in 1970 found that 7.6% of OSMF cases progressed to oral squamous cell carcinoma (OSCC)(8).

**DIAGNOSIS AND EARLY DETECTION**

Diagnosing Oral Submucous Fibrosis (OSF) in its early stages is imperative for effective intervention and prevention of malignant transformation. This comprehensive exploration delves into the diagnostic approaches, tools, and strategies for early detection, drawing insights from recent research articles.

CLINICAL EXAMINATION: The Cornerstone of Diagnosis

The initial diagnosis of OSF relies on a thorough clinical examination by healthcare professionals. The assessment includes evaluating mouth opening, detecting fibrotic bands, noting mucosal changes, and identifying potential ulcerations. A systematic approach, as outlined by studies such as Rajendran R et al. (2020)(6), forms the foundation for recognizing the clinical features indicative of OSF.

HISTOPATHOLOGICAL ANALYSIS: Confirming the Diagnosis(10)

Histopathological examination of a biopsy specimen remains the gold standard for confirming OSF. Characteristic features include submucosal fibrosis, hyalinization, and inflammation. Early stages may show only mild changes, making microscopic analysis crucial for definitive diagnosis. The work of Murti PR et al. (2018)(5) emphasizes the significance of histopathological evaluation in confirming OSF and ruling out other conditions.

Table 2 : HISTOPATHOLOGICAL FEATURES

|  |  |
| --- | --- |
| GRADING/STAGING | HISTOPATHOLOGICAL FEATURES |
| Grade 1 | Inflammatory stage - Coarse edematous collagen, clogged blood vessels, a high concentration of neutrophils, and lymphocytes with myxomatous alterations in the subepithelial, connective tissue layer of the epithelium. |
| Grade 2 | Hyalinization stage – reduced fibroblastic activity, hyalinization of the epithelium collagen in the vicinity of lymphocytes, eosinophils, dilated and clogged blood vessels, alterations in granulation in the muscle layer, and a decrease in inflammatory cells in the subepithelial layer. |
| Grade 3 | Fibrosis stage –comprehensive fibrosis with hyalinization of the collagen from subepithelial to superficial muscle layers with atropic, degerative alterations, obliterated blood vessels, plasma cells, and lymphocytes, and total collagen hyalinization without fibroblast and edema. |
| Grade 4 | Malignant transformation stage – squamous cell carcinoma develops from erythroplakia. |

ADJUNCTIVE DIAGNOSTIC TOOLS: Unveiling Subtle Changes:

Adjunctive diagnostic tools enhance the precision of OSF diagnosis. Imaging techniques, such as ultrasonography and magnetic resonance imaging, aid in visualizing fibrotic changes and assessing the extent of involvement. These tools, as discussed in research articles like Murti PR et al. (2018)(5), provide valuable insights into the submucosal alterations that may not be apparent through clinical examination alone.

SALIVARY BIOMARKERS: Emerging Avenues for Early Detection:

Salivary biomarkers have emerged as potential indicators for early detection and monitoring of OSF. Elevated levels of certain proteins, enzymes, or genetic markers in saliva may signify the presence of OSF even before clinical symptoms become apparent. Research studies, including those conducted by Ghosh S et al. (2018)(4), explore the promising role of salivary biomarkers in the early detection of OSF. Alpha-smooth muscle actin (α-SMA) and E-cadherin were the most frequently reported IHC biomarkers, followed by vascular endothelial growth factor (VEGF), CD34, p53, p63, and Ki67. When compared to OSF and normal patients, oral squamous cell carcinoma originating on an OSF background (OSCC-OSF) showed considerably higher levels of α-SMA, Ki67, CD105, and hTERT(11).

DIGITAL IMAGING TECHNOLOGIES: Transforming Diagnostic Precision:

Advances in digital imaging technologies, such as computer-aided diagnostic systems, hold promise for enhancing diagnostic precision. These technologies utilize algorithms to analyze clinical images and detect subtle changes indicative of OSF. The incorporation of digital tools, as discussed in studies like Sinor PN et al. (2017)(7) , marks a significant step towards early and accurate OSF diagnosis.

**MANAGEMENT**

Effectively managing Oral Submucous Fibrosis (OSF) involves a multidisciplinary approach targeting symptom relief, halting disease progression, and addressing potential complications. This comprehensive exploration delves into various therapeutic interventions, drawing insights from recent research articles.

ARECA NUT CESSATION: Fundamental to Management

The cornerstone of OSF management is the cessation of areca nut and betel quid consumption. Initiatives to promote awareness and facilitate behavioural change are vital components of this strategy. Educational campaigns emphasizing the risks associated with areca nut use, as outlined in studies like Sinor PN et al. (2017)(7), play a pivotal role in encouraging individuals to discontinue this harmful habit.

NUTRITIONAL SUPPLEMENTS: Addressing Deficiencies

Given the association of OSF with nutritional deficiencies, supplementation plays a crucial role. Iron, vitamins, and essential micronutrients are often prescribed to address deficiencies and enhance tissue repair. Nutritional intervention, as discussed by Murti PR et al. (2018)(5) , aims to improve the overall health status of individuals with OSF and mitigate the progression of fibrosis. When evaluating the trace metals copper and zinc in OSMF patients, oral mucosal tissue performs better than serum. The increasing rise in tissue copper levels and the progressive fall in tissue zinc levels, including the chewing habit, are associated with the three clinical stages of OSMF. Higher tissue copper and lower tissue zinc levels were induced by the more processed gutkha(9)

PHYSIOTHERAPY AND STRETCHING EXERCISES: Improving Mouth Opening

Physiotherapy, specifically stretching exercises, is integral to managing trismus associated with OSF. These exercises aim to improve mouth opening and prevent further restriction. A structured physiotherapeutic regimen, as outlined in clinical studies like Rajendran R et al. (2020)(6) , contributes significantly to enhancing the quality of life for individuals with OSF.

MEDICINAL INTERVENTIONS: Pentoxifylline and Collagenase

Pharmacological interventions have shown promise in mitigating fibrotic changes in OSF. Pentoxifylline, known for its anti-fibrotic properties, and collagenase, which aids in tissue remodeling, are among the medications explored. The efficacy of these medicinal interventions is discussed in studies like Sinor PN et al. (2017)(7) , providing valuable insights into their potential role in OSF management.

A)ANTIOXIDANT

1. LYCOPENE : Ernest et al. identified lycopene as a fat-soluble carotenoid in 1959. The main foods that provide humans with lycopene are tomatoes and products made from them. Lycopene is the most effective carotenoid in quenching singlet oxygen, and it achieves this by physically and chemically suppressing free radicals. Because of its special biochemical characteristics, lycopene can shield some types of cellular components from harm caused by extremely reactive oxygen species (ROS), such as hydroxyl and superoxide. It neutralizes ROS twice as well as β-carotene and 10 times as well as α-tocopherol. Lycopene has a daily dietary requirement of 0.5–27 g per person per day. Lycopene was well tolerated within a dose range of 16 to 32 mg per day(12).
2. CURCUMIN : Because of its poor absorption, quick liver metabolism, and quick excretion from the body, curcumin has a low bioavailability. Several formulations of curcumin have been developed to increase systemic bioavailability. These formulations include combining curcumin with additional substances including piperine and phospholipids. Combination of curcumin and piperine (5 mg), which significantly enhanced pain and other OSF clinical symptoms(13)
3. MICRONUTRIENT THERAPY : It was found that swallowing supplements containing micronutrients, such as iron, calcium, copper, zinc, magnesium, and the vitamins A, B complex, C, D, and E, was significantly helpful in reducing OSMF signs and symptoms(8)
4. SPIRULINA AND ALOE VERA : Compared to consuming 5 mg of aloe vera for the same period of time , consuming 500 mg/QD of spirulina for 3 months was linked to a substantial enhancement in mouth opening and a decrease in ulcers, erosions, and vesicles . There was no discernible enhancement in the burning sensation or the pain related to the lesions(8).

B)MEDICINAL TREATMENT

1. STEROIDS : For six months, a grade II and grade III OSMF group experienced a significant enhancement in mouth opening and a burning sensation will reduced after receiving biweekly injections of 4 mg/ml of betamethasone diluted in 1.0 ml of 2% xylocaine on the buccal mucosa using an insulin syringe, with half the dose administered on every side  (8).
2. HYALURONIDASE : For Grade III OSMF patients, an intralesional injection of Hyaluronidase 1500 IU mixed with 1.5 ml of dexamethasone and 0.5 ml of lignocaine hydrochloride administered two times a week for 4 weeks significantly enhancement of mouth opening by lowering the number of painful ulcerations, the burning sensation, and the blanching of the oral mucosa.(8)
3. COLCHICINE + HYALURONIDASE : Colchicine tablets, 1 mg daily, and 0.5 ml intralesional For 12 weeks, hyaluronidase 1500 IU/weekly injection shown a substantial improvement in mouth opening and decreased burning sensation(8).
4. PLACENTAL EXTRACTS : Over the course of 8 weeks, 2 ml intralesional placental extract combined with 2 ml of 2% lignocaine HCL once a week resulted in an average enhancement in mouth opening and a considerable decrease in burning sensation(8).
5. PENTOXIFYLLINE : After taking 400 mg/TID of Pentoxifylline tablets for seven months, there was a considerable enhancement in the following symptoms: burning sensation in the mouth, tinnitus, tongue protrusion, relief from perioral fibrotic bands, difficulty speaking, and difficulty swallowing(8).

SURGICAL OPTIONS: Release of Fibrotic Bands:

In advanced cases of OSF, where fibrotic bands severely restrict mouth opening, surgical intervention may be considered. Release of fibrotic bands through surgical procedures aims to improve mouth mobility and alleviate associated symptoms. The appropriateness of surgical interventions, as highlighted by Rajendran R et al. (2020)(6) , is determined based on the severity and extent of fibrosis.

The steps that comprise the treatment regimens derived from the review can be roughly classified as follows(15)

Step 1: Use a scalpel or laser to remove fibrotic bands.

Step 2: Covering the mucosal defect with collagen membranes, flaps, and grafts.

Step 3: Coronadoidectomies and masticatory muscle myotomies were among the adjunctive techniques performed during surgery.

Step 4: Medication, nutritional supplements, and oral physiotherapy following surgery.

A)PRIMARY EXCISION(15)

According to Venkatesh V Kamath , the scalpel was a frequent tool used for primary excision. The precise boundaries of band excision, along with its direction and extent, were not specified. It is commonly known that circumferential bands that follow the outline are more common on the soft palate, diffuse fibrosis without defined bands is common in the tongue, and vertical bands are more common in the buccal mucosa. While the majority of the study concluded that “excision of palpable bands” as the surgical intervention’s preparatory phase, a few did describe the extent of vertical excision as the parotid papilla level.

The ErYCCG laser , KTP 532 , and diode lasers were the most often used lasers. Rather of being the result of a methodical selection process, the choice of lasers appears to have been influenced by what was available in the surgical unit. Only cases involving the buccal mucosa and restricted fibrosis areas appeared to have undergone laser excision. There were no reports of laser usage in additional oral locations. There were no additional procedures performed in addition to routine postoperative physiotherapy while using lasers. Laser excision was shown to be both good and excellent in terms of efficacy, with follow-ups lasting no longer than six months.

B)INTERPOSITIONAL FLAPS (GRAFTS)(15)

The most common surgical intervention in OSF has been the use of interpositional grafts in band excision. Distinct flaps and local flaps. Local flaps suggest pedicle attachments that transfer donor sites from the head and neck region to the mouth cavity. Free flaps with arteriovenous anastomoses from donor sites in the arm and thigh are examples of distant flaps.

LOCAL FLAPS

1.Intraoral flaps

A)Tongue flaps

B)Palatal island flaps

2.Extraoral flaps

A)Buccal fat pad

B)Nasolabial flap

C)Temporalis fascia flap

Split skin grafts (SSG), collagen membranes and artificial dermis, human placenta and amnion have been the common materials preferred in the grafting of mucomuscular defects in the surgical management of OSMF

FOLLOW-UP AND SURVEILLANCE FOR MALIGNANT TRANSFORMATION:

Long-term follow-up and surveillance are essential components of OSF management, considering its potential for malignant transformation. Regular clinical examinations, imaging studies, and biopsies, as emphasized in studies like Maher R et al. (2019)(1), help in identifying any signs of dysplasia or malignant changes, enabling timely intervention.

**PREVENTION**

Preventing the onset and progression of Oral Submucous Fibrosis (OSF) involves comprehensive strategies targeting its multifactorial etiology. This exploration delves into preventive measures, drawing insights from recent research articles.

PUBLIC HEALTH AWARENESS CAMPAIGNS:

Education and awareness campaigns form the foundation of OSF prevention. Informing communities about the harmful effects of areca nut and betel quid through various media channels can contribute to behavioral change7.

COMMUNITY ENGAGEMENT AND COUNSELING:

SCHOOL-BASED EDUCATIONAL PROGRAMS:

NUTRITIONAL COUNSELING AND SUPPLEMENTATION:

NICOTINE REPLACEMENT THERAPY

The available replacements are nicotine gums, nicotine patch. Nicotine inhaler, nicotine nasal spray. Nicotine lozenges. It is contraindicated for Pregnancy, lactation, cardiovascular disease, peripheral vascular disease, endocrine disorder, inflammation of mouth and throat, oesophagitis, gastric ulcers, and diabetes. Patient need the greatest support during first 3 days and first 3 weeks after stopping the use of tobacco. The withdrawal symptoms are craving for tobacco, depressed mood, insomnia, irritability, frustration, anxiety, difficulty in concentration, restlessness, decreased heart rate, increased appetite and weight gain.

**CONCLUSION**

Oral Submucous Fibrosis remains a challenging health concern, necessitating a holistic understanding of its etiology, clinical features, diagnosis, and management. Ongoing research continues to unravel the complexities associated with OSF, shedding light on potential therapeutic targets and preventive strategies. A multidisciplinary approach involving healthcare professionals, researchers, and policymakers is crucial to mitigate the impact of OSF on global oral health.

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