Review Article

Oral submucous fibrosis

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ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic, complex potentially malignant disorder. It is characterized by juxtaepithelial inflammatory reaction. It is characterized by inflammation and a progressive fibrosis of the lamina propria and deeper connective tissues. The etiology is multifactorial tobacco, areca nut chewing, consumption of chilies, genetics, and nutritional deficiency. There is a burning sensation followed by blisters, stomatitis, stiffness of tissues, and difficulty in mouth opening. This review attempts to give a comprehensive outline of the classification, clinical and histopathological features, etiology, pathogenesis, and treatment of OSMF.

KEY WORDS: Classification, Etiology, Oral submucous fibrosis, Pathogenesis, Treatment

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic progressive scarring disease[1] of the oral cavity and oropharynx characterized by fibroelastic changes and inflammation of the mucosa. The condition was described first by Schwartz (1952) while examining five Indian women from Kenya, to which he ascribed the descriptive term "atrophia idiopathica (tropica) mucosae oris." It is an emerging health concern, creating a burning sensation followed by blisters, stomatitis, stiffness of tissues,[2] and a progressive inability to open the mouth.[3]

ETIOLOGY

OSMF has a multifactorial etiology including:[4]

Areca Nut

The term areca nut is used to denote the unhusked whole fruit of the areca nut tree. Arecoline, arecaidine, guvacine, and guvacoline are the four alkaloids seen in areca nut. Of which arecoline is the main agent. They promote salivation, stain the saliva red, and act as stimulants.[5,6] Cyanoethyl is formed in the metabolism of this areca nut-specific nitrosamine, which binds with O-methylguanine in DNA. Malignant transformation is seen to result due to the prolonged exposure to this irritant. Recently suggested that pathogenesis of OSMF is by dual action of areca nut. It is suggested that arecoline not only stimulates fibroblastic proliferation and collagen synthesis but also decreases its breakdown.[7]

Areca and Slaked Lime

OSMF may be caused by the amount of tannic acid contained in the betel nut, the influence of mixed calcium powder, and the conditional action of arecoline content in betel nut, affecting the vascular supply of oral mucosa and causing neurotropic disorder. Hydrolysis of arecoline to arecaidine occurs when slaked lime is added to areca nut making this agent available in the oral environment.

Tobacco and Lime

These act as local irritants. Pan masala, gutka, and mawa (areca, tobacco, and lime) have high concentrates of areca nut per chew and appear to cause OSMF more rapidly than by self-prepared conventional betel quid which contains smaller amounts of areca nut. Lime acts to keep the active ingredient in its free base or alkaline form to enter the bloodstream through sublingual absorption.[5]

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Chilies

Ingestion of chilies is common in the Indian continent. Capsaicin, being the active ingredient of chilies, is considered as a source of allergen for causing OSMF.[7]

Nutritional Deficiency

A subclinical Vitamin B complex deficiency has been suspected in cases of OSMF with vesiculations and ulcerations of oral cavity.[1]

Betel Quid

It is the primary cause of OSMF. Betel quid chewing is a habit practiced predominantly in Southeast Asia and India that dates back for thousands of years. The mixture of this quid or chew is a combination of areca nut (fruit of *Areca catechu* palm tree) and betel leaf (from the Piper betel, a pepper shrub), tobacco, slaked lime, and catechu (extract from the *Acacia catechu* tree). Lime acts to keep the active ingredient in its free base or alkaline form to enter the bloodstream through sublingual absorption. Arecoline, arecadidine, guvacine, and guvacoline are alkaloids found in areca nut that promotes salivation, stains the saliva red, and acts as stimulants.[5,6]

CLASSIFICATION

Classification Based on Clinical Features

1. JV Desa (1957) divided OSMF into three stages as follows:[8]
   - Stage 1: Stomatitis and vesiculation.
   - Stage 2: Fibrosis.
   - Stage 3: As its sequelae.

2. Pindborg JJ (1989) divided OSMF into three stages:[9]
   - Stage 1: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation, and 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 deficit may occur due to the involvement of tongue and the Eustachian tube.

3. SK Katheria *et al*. (1992) have given different scores assigned to the patients on the basis of mouth opening between upper and lower central incisors as follows:[10]
   - Score 0: Mouth opening is 41 mm or more.
   - Score 1: Mouth opening is 37–40 mm.
   - Score 2: Mouth opening is 33–36 mm.
   - Score 3: Mouth opening is 29–32 mm.
   - Score 4: Mouth opening is 25–28 mm.
   - Score 5: Mouth opening is 21–24 mm.
   - Score 6: Mouth opening is 17–20 mm.
   - Score 7: Mouth opening is 13–16 mm.
   - Score 8: Mouth opening is 9–12 mm.
   - Score 9: Mouth opening is 5–8 mm.
   - Score 10: Mouth opening is 0–4 mm.

4. Nagesh and Bailoor (1993) based on diagnosis:[11]
   - Stage I early OSMF: Mild blanching, no restriction in mouth opening (normal distance between central incisor tips: Males 35–45 mm and females 30–42 mm), no restriction tongue protrusion. Males 5–6 cm and females 4.5–5.5 cm. Mean value of cheek flexibility for males 1.2 cm and females 1.08 cm.
   - Stage II moderate OSMF: Moderate-to-severe blanching, mouth opening reduced by 33%, cheek flexibility also demonstrably reduced, burning sensation also in the absence of stimuli, palpable bands felt. Lymphadenopathy either unilateral or bilateral and demonstrable anemia on hematological examination.
   - Stage III severe OSMF: Burning sensation is very severe. Patient unable to do day-to-day work, more than 66% reduction in the mouth opening, cheek flexibility, and tongue protrusion. Tongue may appear fixed. Ulcerative lesions may appear on the cheek, thick palpable bands, and lymphadenopathy bilaterally evident.

5. Lai DR (1995) divided OSMF based on the interincisal distance as follows:[9]
   - Group A: >35 mm
   - Group B: Between 30 and 35 mm
   - Group C: Between 20 and 30 mm
   - Group D: <20 mm.

6. R Maher *et al*. (1996) had given criteria for evaluation of interincisal distance as an objective criterion of the severity of OSMF in Karachi, Pakistan. He divided the intraoral regions into eight subregions and grouped into three categories.[12]
   - Involvement of one-third or less of the oral cavity (if three or less of the above sites are involved).
   - Involvement of one–two-thirds of the oral cavity (if four to six intraoral sited are involved).
   - Involvement of more than two-thirds of the oral cavity (if more than six intraoral sites are involved).

7. Wahi P N *et al*. (1996) classified OSMF based on clinical severity and extent of involvement into three groups:[13]
   - Group 1: No symptoms referable to buccal mucosa, focal pallor/whitish discoloration of mucosa.
   - Group 2: Symptoms of the soreness of mucosa increased sensitivity to chili, lesions diffuse, white, extensive, indurated involving one, or anatomical sites.

- Group 3: Trismus, stretching at angles of mouth, and altered pronunciation. Firm mucosal bands. Surface might me fissured or ulcerated.

8. Bhatt AP and Dholaksha LM (1971) clinically grouped the patients into three grades:[14]
   - Grade 1: Comprised mild and early cases with a very slight fibrous bands and little close the mouth.
   - Grade 2: Moderately pronounced symptoms of the diseases with fibrous banding extending from cheek to palate area.
   - Grade 3: Markedly excessive amount of fibrous band involving cheek, palate, uvula, tongue, and lips and restrict mouth opening.

9. Ahuja SS and Agarwal GD (1971) classified depending on extent and type of fibrosis:[15]
   - Class 1 - Localized fibrous bands in the cheek extending from the superior to inferior vestibular fornix of one both sides. Bands are usually located in the premolar region and the second molar region.
   - Class 2 - Generalized diffuse hardening of the subepithelial tissues. Thus, hardening usually extends from the cheek and hard palate to soft palate, uvula, and the pillars of the fauces. In occasional cases, the hardening might extend to the lining mucous membrane of the pharynx.
   - Class 3 - Combination of above 2 types where the fibrous bands are associated with a generalized diffuse form of submucous fibrosis.

10. Racher SK classified OSMF based on habits: The patients can be grouped into three stages:[16,17]
    - Stage I: Stage of stomatitis and vesiculation: Characterized by recurrent stomatitis and vesiculation. Patient complains of burning sensation in the mouth and inability to eat pungent food. The examination reveals vesicle on the palate. They may rupture and a superficial ulceration may be seen. Some amount of fibrosis can be seen.
    - Stage-II: Stage of fibrosis: There is inability to open the mouth completely and stiffness in mastication. As disease advances, there is difficulty in blowing out cheek and difficulty in protruding the tongue. On examination, there is increasing fibrosis in the submucosa. Mucosa is blanched and white, lips and cheeks are stiff. The salivary glands are normal. Dorsum of tongue may show atrophy of papillae. Blanching and stiffness of the mucosa of the floor of the mouth is less marked than that seen in the lips, cheek, and palate. Larynx is free from disease and respiration is not affected.
    - Stage-III: Stage of sequelae and complications: Leukoplakia changes in the mucosa. An ulcerating malignant lesion may be seen involving the cheek, oropharynx, and tongue. There is evidence to suggest that OSMF is a precancerous condition. The mechanism involved in the development of oral cancer in patients with OSMF is not yet understood. It is generally accepted that atrophic epithelium is more likely to undergo malignant changes than epithelium of normal thickness. Thus, the patient with OSMF may be predisposed to develop oral cancer under the influence of carcinogens.

11. Gupta DS *et al*. (1980): Clinically classified four stages of submucosal fibrosis as per the increasing intensity of trismus: [11]
    - Very early stage: The patients complained by burning sensation in the mouth or ulceration without difficulty in opening the mouth.
    - Early stage: Along with symptoms of burning, the patient complained of slight difficulty in opening the mouth.
    - Moderately advanced stage: The trismus is marked to such an extent that patient cannot open his mouth more than two fingers. Patient, therefore, experiences difficulty in mastication.
    - Advanced stage: Patient is undernourished, anemic and has a marked degree of trismus.

12. Ranganathan K *et al*. (2001) divided OSMF based on mouth opening as follows:[9,18]
    - Group I: Only symptoms, with no demonstrable restriction of mouth opening.
    - Group II: Limited mouth opening 20 mm and above.
    - Group III: Mouth opening <20 mm.
    - Group IV: OSMF advanced with limited mouth opening. Precancerous or cancerous changes seen throughout the mucosa.

13. Rajendran R (2003) reported the clinical features of OSMF as follows:[9]
    - Early OSF: Burning sensation in the mouth. Blisters especially on the palate, ulceration or recurrent generalized inflammation of oral mucosa, excessive salivation, defective gustatory sensation, and dryness of mouth.
    - Advanced OSF: Blanched and slightly opaque mucosa, fibrous bands in buccal mucosa running in vertical direction. Palate and faucial pillars are the areas first involved. Gradual impairment of tongue movement and difficulty in mouth opening.

14. Tinky Bose and Anita Balan (2007) had given clinical classification, categorized the patients into three groups based on their clinical presentations:[19]
    - Group A - mild cases: Only occasional symptoms, pallor, vesicle formation, presence of one or two solitary palpable bands, loss of elasticity of mucosa, and variable tongue involvement with

protrusion beyond vermillion border. Mouth opening >3 cm.

- Group B - moderate cases: Symptoms of the soreness of mucosa or increased sensitivity to chilies, diffuse involvement of the mucosa, blanched appearance, buccal in mucosa tough and inelastic fibrous bands palpable, considerable restriction of mouth opening (1.5–3 cm), and variable tongue movement.
- Group C - severe cases: Symptoms more severe, broad fibrous bands palpable, blanched opaque mucosa, rigidity of mucosa, very little opening of mouth (<1.5 cm), depapillated tongue, and protrusion of tongue very much restricted.

15. Kiran Kumar *et al*. (2007) categorized three clinical stages of OSMF on the basis of mouth opening as follows: [20]
    - Stage I: Mouth opening >45 mm.
    - Stage II: Restricted mouth opening 20–44 mm.
    - Stage III: Mouth opening <20 mm.

16. Haider *et al*. (2011) study based on severity of the disease with functional staging and objective measures interincisal opening:[21]

Clinical staging:

- Stage 1: Facial bands only.
- Stage 2: Facial and buccal bands.
- Stage 3: Facial and labial bands.

Functional stage:

- Stage A: Mouth opening 13–20 mm.
- Stage B: Mouth opening 10–11 mm.
- Stage C: Mouth opening <10 mm.

17. Chandramam More *et al*. (2011):[22]

Clinical staging:

- Stage 1 (SI): Stomatitis and/or blanching of oral mucosa.
- Stage 2 (S2): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, with/ without stomatitis.
- Stage 3 (S3): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, and in any other parts of oral cavity, with/without stomatitis.
- Stage 4 (S4) as follows:
    A. Anyone of the above stage along with other potentially malignant disorders, for example, oral leukoplakia, oral erythroplakia, etc.
    B. Anyone of the above stages along with oral carcinoma.

Functional staging:

- Ml: Interincisal mouth opening up to or >35 mm.
- M2: Interincisal mouth opening between 25 and 35 mm.
- M3: Interincisal mouth opening between 15 and 25 mm.
- -M4: Interincisal mouth opening less than IS mm.

Classifications Based on Histopathological Features of OSMF

1. Pindborg JJ and Sirsat SM (1966) were the first to divide OSMF depending only on histopathological features alone are as follows:[9]

- 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: Juxtaepithelial 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. Blood vessels 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 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.

2. Utsimomiya H, Tilakratne Wm, Oshiro K *et al*. (2005) histologically divided OSMF based on the concept of Pindborg and Sirsat and modified it as follows:[4]
    - Early stage: Large number of lymphocytes in subepithelial, connective tissue, zone along with myxedematous changes.
    - Intermediate stage: Granulation changes close to the muscle layer and hyalinization appears in subepithelial zone where blood vessels are compressed by fibrous bundles. Reduced inflammatory cells in subepithelial layer.
    - Advanced stage: Inflammatory cell infiltrate hardly seen. Number of blood vessels dramatically small in subepithelial zone/marked fibrous areas with hyaline changes extending from subepithelial to superficial muscle layers. Atrophic, degenerative changes start in muscle fibers.

3. Kiran Kumar *et al*. (2007) proposed histological grading as follows:
    - Grade 1: Loose, thick, and thin fibers.
    - Grade II: Loose or thick fibers with partial hyalinization.
    - Grade III: Complete hyalinization.

Classification Based on Clinical and Histopathological Features

1. Khanna JN and Andrade NN (1995) developed a group classification system for the surgical management of OSMF.[23]
   - Group I: Very early cases: Common symptom is burning sensation in the mouth, acute ulceration, and recurrent stomatitis and not associated with mouth opening limitation. Histology: Fine fibrillar collagen network interspersed with marked edema, blood vessels dilated and congested, large aggregate of plump young fibroblasts present with abundant cytoplasm, inflammatory cells mainly consist of polymorphonuclear leukocytes with few eosinophils. The epithelium is normal.
   - Group II: Early cases - buccal mucosa appears mottled and marble like, widespread sheets of fibrosis palpable, interincisal distance of 26–35 mm. Histology: Juxtaepithelial hyalinization present, collagen present as thickened but separate bundles, blood vessels dilated and congested, young fibroblasts seen in moderate number, inflammatory cells mainly consist of polymorphonuclear leukocytes with few eosinophils and occasional plasma cells, flattening or shortening of epithelial rete pegs evident with varying degree of keratinization.
   - Group III: Moderately advanced cases - Trismus, interincisal distance of 15–25 mm, buccal mucosa appeal's pale firmly attached to underlying tissues, atrophy of vermilion border, vertical fibrous bands palpable at the soft palate, pterygomandibular raphe, and anterior faucial pillars.
   - Histology: Juxtaepithelial hyalinization present, thickened collagen bundles, residual edema, constricted blood vessels, mature fibroblasts with scanty cytoplasm and spindle-shaped nuclei, inflammatory exudates which consist of lymphocytes and plasma cells, epithelium markedly atrophic with loss of rete pegs, muscle fibers seen with thickened and dense collagen fibers.
   - Group IVA: Advanced cases - severe trismus, interincisal distance of <15 mm, thickened faucial pillars, shrunken uvula, restricted tongue movement, and presence of circular band around entire lip and mouth.
   - Group IVB: Advanced cases - presence of hyperkeratotic leukoplakia and/or squamous cell carcinoma.
   - Histology: Collagen hyalinized smooth sheet, extensive fibrosis, obliterated the mucosal blood vessels, eliminated melanocytes, absent fibroblasts within the hyalinized zones, total loss of epithelial rete pegs, presence of mild-to-moderate atypia, and extensive degeneration of muscle fibers.

PATHOGENESIS

Quid has been defined as a substance, or mixture of substances, placed in the mouth or chewed and remaining in contact with the mucosa, usually containing one or both of the two basic ingredients, tobacco, and/or areca nut, in raw or any manufactured or processed form.[24] In most areas, betel quid consists of a mixture of areca nut (betel nut), slaked lime, catechu, and several condiments according to taste, wrapped in a betel leaf. The chewing habit varies among individuals, it is usually placed in the buccal vestibule for 15 min to an hour, repeated 5–6 times a day. There is a continuous contact between the mixture and the mucosa. Over a period of time, chronic inflammation sets in.[25-27] This leads to atrophy and ulceration of the oral mucosa. In inflammation, activated T-cells and macrophages are present. Chemical mediators of inflammation are released including prostaglandins, cytokines interleukin 6, tumor necrosis factor, and interferon α (10) and growth factors like TGF-β.[28]

COLLAGEN PRODUCTION PATHWAY

The three main events that are modulated by TGF-β, which favors the collagen production are [Figure 1]:

1. Activation of procollagen genes;
2. Elevation of procollagen proteinases levels:
   a. Procollagen C-proteinase/bone morphogenetic protein1 (BMP1) and
   b. procollagen N-proteinase;
3. Upregulation of lysyl oxidase (LOX) activity.

ACTIVATION OF PROCOLLAGEN GENES

The activation of procollagen genes by TGF-β causes an increased expression of procollagen genes and, hence, increases collagen level in OSMF. Procollagen monomeric chains are formed by the transcription and translation of procollagen genes. Elevation of procollagen proteinases cleaves C-terminal which plays an essential role in pathogenesis of OSMF. After this cleavage, the collagen units form spontaneously into fibrils.[29,30]

UPREGULATION OF LOX

An essential enzyme for final collagen fibers processing into a stabilized covalently cross-linked mature fibrillar form that has proteolytic resistance is LOX. The enzyme LOX is found to be upregulated in OSMF. LOX is a copper-dependent enzyme and plays a key role in collagen synthesis and its cross-

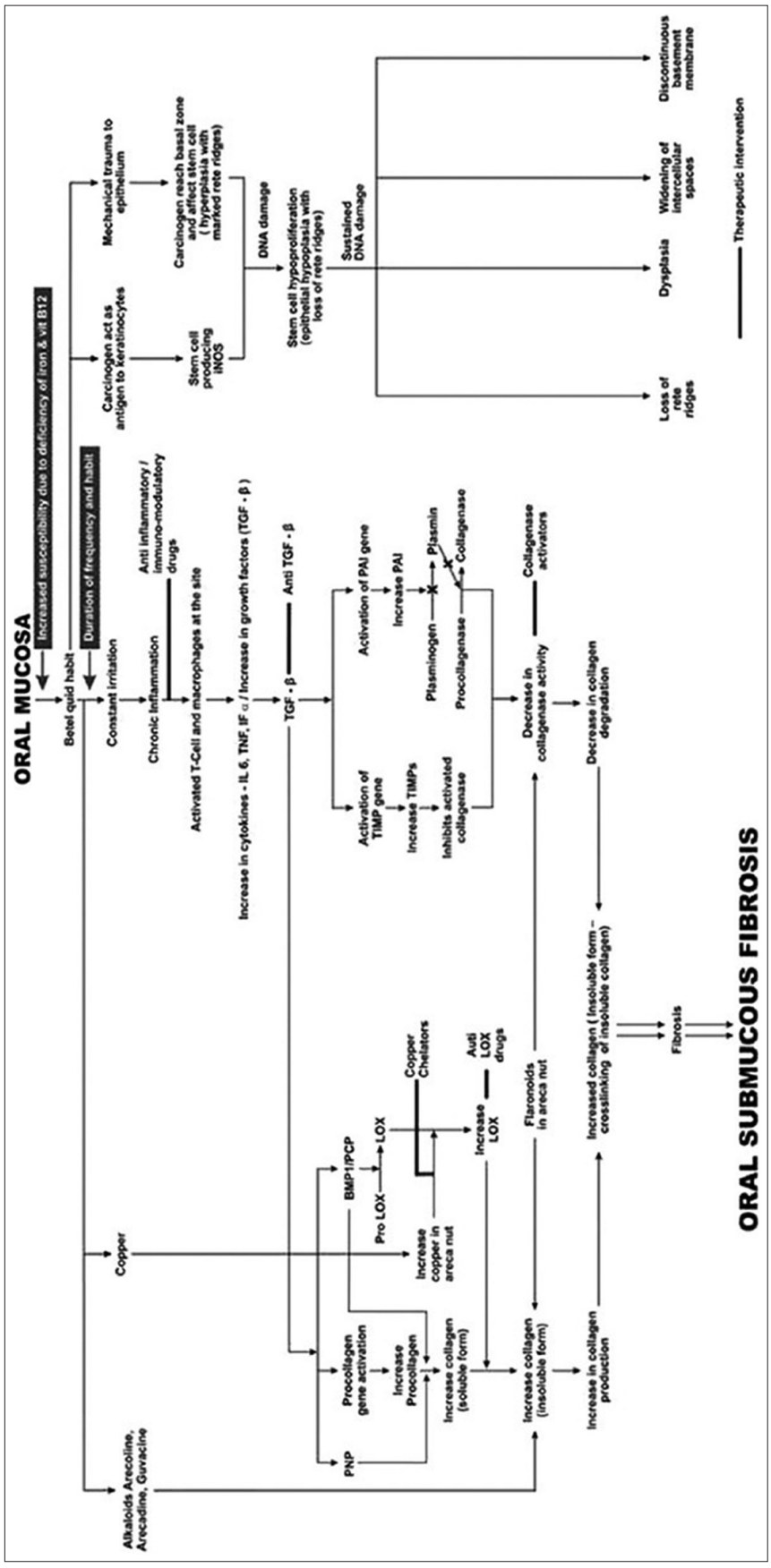

Figure 1: Molecular pathogenesis of oral submucous fibrosis (OSMF). Courtesy of Thukanaykanpalayam Ragunathan Yoithapprabhunath *et al.*; Pathogenesis and therapeutic intervention of OSMF

linkage. Prolysyl oxidase is the precursor of LOX and conversion is mediated by BMP1.[31] During the biosynthesis of LOX, copper is incorporated into LOX.[32] The high copper content in areca nut and chewing of the betel quid increases soluble copper levels in oral fluids. This increased level of soluble copper could act as an important factor in OSMF by stimulating fibrogenesis through upregulation of LOX activity. The expression of LOX is regulated by various factors, among which TGF-β is considered to be an important factor. TGF-β has been found to strongly promote the expression of LOX both at the mRNA and protein levels. LOX activity is important for the formation of insoluble collagen due to cross-linking. Increased levels and activity of LOX as a result of increased BMP and copper levels, leads to a fibrotic condition as present in Oral submucous fibrosis.[33,34]

COLLAGEN DEGRADATION PATHWAY

There are two main events modulated by TGF-β, which decreases the collagen degradation:

i. Activation of tissue inhibitor of matrix metalloproteinase gene (TIMPs) and
ii. Activation of plasminogen activator inhibitor (PAI) gene.

ACTIVATION OF TIMPs

TIMPs are specific inhibitors of MMPs that play an essential role in controlling their local activities in tissues. ECM is a process that occurs in normal tissues during development and wound healing, as well as in inflamed tissues during rheumatoid arthritis and during tumor invasion and metastasis,[35] and TIMPs are the biological regulators. In OSMF, there is increased production of TIMPs,[36,37] thereby inhibiting collagenase and decreasing collagen degradation. TIMP1 gene expression is induced by TGF-β and it has been identified as one of the definite early induced TGF-β target genes in fibroblasts.[30] The exact mechanism of regulation is not known. Thus, TGF-β decreases the collagen degradation by activating TIMP gene, thereby enhancing its level resulting in inhibition of the activated collagenases.

ACTIVATION OF PAI

In OSMF, the plasminogen activation process is inhibited, as there is an increase in PAI1. Different cytokines regulate PAI, among, which TGF-β plays an important role. TGF-β has been shown to stimulate PAI1 secretion in various cell lines and *in vivo*. The inhibition of the existing collagenase and decreased generation of active collagenase together results in a marked decrease in collagen degradation and a resultant buildup of collagen in OSMF.[38]

EPIDEMIOLOGY

Worldwide, it is estimated that 2.5 million people are affected with OSMF, most of the cases in the Indian subcontinent, especially southern India. The rate varies from 0.2% to 2.3% in males and 1.2–4.5% in females in Indian communities.[25] An epidemiological survey done a decade ago indicated not <250,000 cases reported in India and suggested an overall prevalence of up to 0–4% in places at Kerala.[39]

MALIGNANT TRANSFORMATION

The malignant potential of OSMF was first described by Paymaster in 1956, the rate of which has been estimated to be 7–13% recently. Many follow-up studies had been conducted so far to identify the important aspects in malignant transformation. Large exophytic lesions are seen in minority cases of transformation which are clinically typical OSCC without showing any histological evidence of invasion. Molecular markers are believed to be helpful in early diagnosis and expecting therapeutic implications for carcinogenesis in the background of OSF.[40]

TREATEMENT

The treatment of patients with OSMF depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with OSMF present with moderate-to-severe disease. Moderate-to-severe OSMF is irreversible. Medical treatment is symptomatic and predominantly aimed at improving mouth movements.

- Steroids: In patients with moderate OSMF, weekly submucosal intralesional injections or topical application of steroids may help prevent further damage.
- Placental extracts: It has anti-inflammatory effect,[41] hence, preventing or inhibiting mucosal damage. Cessation of the habit and submucosal administration of aqueous extract of healthy human placental extract (placentrex) have shown marked improvement of the condition.[42]
- Hyaluronidase: The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone.[43]
- IFN-gamma: This plays a role in the treatment of patients with OSMF due to its immunoregulatory effect. IFN-gamma is a known antifibrotic cytokine. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with OSMF, and intralesional injections of the cytokine may have a significant therapeutic effect on OSMF.[44]
- Lycopene: Newer studies highlight the benefit of this oral nutritional supplement at a daily dose of 16 mg. Mouth opening was better improved.[45]

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