



## Review Article

## Oral submucous fibrosis: Histopathogenesis

Juveria Ahmed<sup>1\*</sup>, Abhiney Puri<sup>1</sup>, Rajat Nangia<sup>1</sup>, Safiya Bhat<sup>1</sup>,  
Akshita Pasbola<sup>1</sup>

<sup>1</sup>Dept. of Dentistry, Himachal Institute of Dental Science, Himachal Pradesh, India



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## ABSTRACT

Oral submucosal fibrosis (OSMF) is a precancerous condition of the oral cavity caused by the development of inflammation and fibrosis in the submucosal tissue, causing symptoms of tension and trismus. OSMF remains a concern for healthcare providers due to its easy transmission and uncertain distribution. Over the years, many classifications based on clinical, histopathological, or functional basis have been documented in the medical literature. However, none of these classifications are universally accepted. Each distribution has advantages and disadvantages. It strives to provide and update information on the OSMF classification system to help clinicians, researchers, and researchers classify these diseases for early diagnosis, and treatment time, and reducing the number of deaths. Pathogenesis and treatment are also discussed.

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## 1. Introduction

Oral submucosal fibrosis (OSMF) is a chronic disease of the oral cavity caused by epithelial and subepithelial inflammatory reactions and subsequent fibroblastic changes in the submucosa.<sup>1</sup> Excessive use of nuts can cause fibrosis due to increased connectivity.<sup>2</sup> This disease is more common in South Asian immigrants from South Asian countries or other parts of the world who have a habit of chewing the fruit.<sup>3</sup> Iron, zinc, copper, etc. Nutritional deficiencies in vitamins and minerals are thought to be essential for OSMF.<sup>4</sup>

The lesion begins as an inflammatory condition, and as it progresses, the vascularity of the involved area declines, blanching of the afflicted oral mucosa occurs, and fibrosis of the concerned areas is noted. In the early stages, the patient may complain of a burning feeling or discomfort in the mouth, and patches of tiny vesicles or ulcers may be visible on visual examination. Fibrous bands grow as the

condition worsens, causing limited mouth opening, trouble swallowing, trouble moving the tongue, etc.<sup>5</sup>

They show that young people have a habit of mixing areca nuts and tobacco. An increase in OSMF of up to 85% has been reported in patients under 35 years of age. Chewing areca nuts or betelnuts is an important habit among Indians. It is said to be one of the main causes of OSMF and can lead to poor oral health. The combination of habits such as smoking, alcohol consumption, and betel quid increases the incidence and adverse effects of OSMF compared to the use of areca nut alone.

## 1.1. Molecular pathogenesis

Malignancies Essential components included within the pathogenesis of OSMF can be separated into four steps:

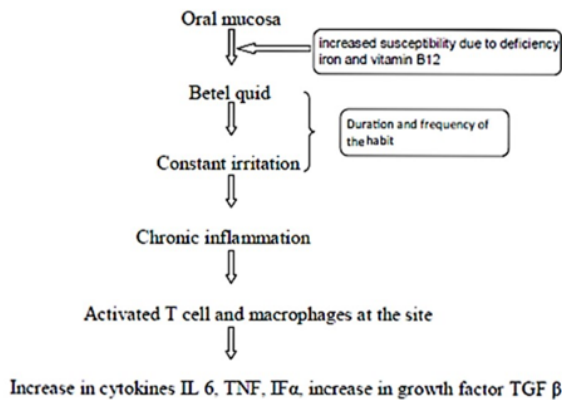
1. Sensitive diseases occur at the location of betel quid placement
2. Increase collagen synthesis
3. Collagen Crosslinking
4. Reduces collagen degradation

\* Corresponding author.

E-mail address: [habjuv1828@gmail.com](mailto:habjuv1828@gmail.com) (J. Ahmed).

## 2. Sensitive diseases occur at the location of betel quid placement

This micro-injury caused by continuous rubbing of the rough fiber of the areca nut facilitates the diffusion of betel juice alkaloids and flavonoids in the subepithelial connective tissue, leading to inflammatory cell infiltration of the adjacent epithelium. Inflammation is categorized by the occurrence of triggered T cells, macrophages, etc. Synthesis of various inflammatory mediators such as prostaglandins and growth factors such as TGF-beta. Cytokines such as interleukin-6 (IL-6), tumor necrosis factor (TNF), interferon- $\alpha$ , and beta-TGF (bTGF) are made at the site of inflammation. Increases collagen production and reduces collagen breakdown, and is a regulator of extracellular matrix (ECM) assembly and remodeling. TGF-beta 1 is a key regulator of ECM assembly and remodeling.<sup>6</sup>



**Figure 1:** The initial events of the disease process due to betel-quid habit, which causes continuous irritation

### 2.1. Increase collagen synthesis

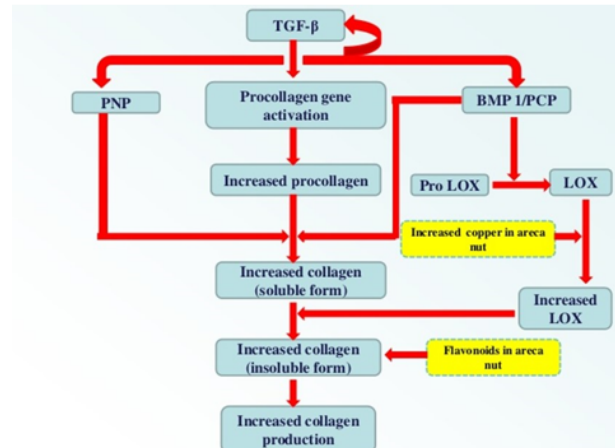
The three important events that are modulated via TGF:

1. Activation of procollagen genes
2. Elevation of procollagen proteinases degrees procollagen C-proteinases (PCP)/ bone morphogenetic protein 1 (BMP1) and procollagen N-proteinases (PNP)
3. Up-law of Lysyl oxidase (LOX) pastime.<sup>7</sup>

### 2.2. Activation of procollagen genes

The genes COL1A2, COL3A1, COL6A1, COL6A3, and COL7A1, were diagnosed as particular TGF-beta goals. The activation of procollagen genes through TGF-beta outcomes in the multiplied expression of procollagen genes and hence will increase collagen levels in OSMF. The activation of collagen I and VII collagen gene expression via TGF-beta has been cited. TGF-beta might also play a vital role in

inducing fibrotic tissue formation, whilst connective tissue increase element (CTGF) is vital in controlling fibrosis. A boom in CTGF synthesis during areca nut chewing is seen at the side of an increase in neighborhood TGF-beta awareness because of irritation found in OSMF.<sup>8</sup>



**Figure 2:** Flowchart displaying collagen production pathway

### 2.3. Elevation of procollagen proteinases degree

An essential role is performed with the aid of procollagen proteinases in the processing of seasoned collagen precursors into collagen fibers which can be soluble. There are varieties of proteinases that cleave the N- and C terminal respectively PNP and PCP.<sup>9</sup>

### 2.4. Up-regulation of LOX

There's an Upregulation of the enzyme Lysyl Oxidase in OSMF. Lysyl oxidase is a copper-structured enzyme and plays an enormous position in collagen synthesis and its go linkage. The fibroblast in OSMF has not handiest multiplied Lysyl oxidase interest but also potentiates particular growth characteristics. The LOX pastime is crucial for insoluble collagen due to cross-link growing older which offers tensile energy and mechanical houses to the fiber making it immune to proteolysis, resulting in growing fibrotic circumstances in OSMF.<sup>8</sup>

### 2.5. Collagen crosslinking

There are essential events modulated by using TGF:

1. Enactment of tissue inhibitor of matrix metalloproteinase gene. (TIMPs).
2. Enactment of plasminogen activator inhibitor gene (PAI).

### 2.6. Enactment of tissue inhibitor of matrix metalloproteinase gene (TIMPs)

Matrix metalloproteinases (MMPs) are a family matrix degrading protease. they're endopeptidases that play an essential position in tissue remodelling by degrading ECM, both in fitness and sickness. At gift, many human MMPS has been pronounced however MMP1, MMP8, and MMP13 are recognized for collagen breakdown i.e., collagenases.

Those collagenases are activated by way of chemicals along with loose radicals fashioned in the course of the oxidative burst of leukocytes and proteinases. Collagenases are the principal human enzyme that cleaves local fibrillar collagen. Flavonoid, catechin, and tannin in betel nuts motivate collagen fibers to pass-link, making them much less at risk of collagenases.

These outcomes in increased fibrosis due to both increased collagen production and reduced breakdown. TIMPs are unique inhibitors of MMPs and play a critical role in controlling their neighbourhood activities inside the tissue. 4 types TIMP-1, TIPM-2, TIMP-three, and TIPM-four have been diagnosed in vertebrates. TIMP-1 is thought for its position within the organic regulator of the turnover of ECM.

They have a large role in regulating mobile growth and apoptosis. Boom expression of TIMPs has been pronounced in OSMF; as an end result, they inhibit collagenases and decrease collagen degradation charge.<sup>8</sup>

### 2.7. Enactment of plasminogen activator inhibitor gene (PAI)

The plasminogen (plg) activation device is an extracellular proteolytic device, which performs a critical position in tissue remodeling. The primary characteristic of this device is the conversion of the zymogen, plug to the active serine protease, plasmin. Plasmin is answerable for the activation of seasoned MMPs. Activated MMPs can contribute to processing other MMPs.

As plasmin promotes the formation of active MMPs, it facilitates the degradation of collagen. In OSMF, the plug activation system is inhibited, as there's a boom in PAI. The inhibition of the prevailing collagenases and decreased production of active collagenases collectively bring about a hanging lower in collagen degradation and a resultant build-up of collagen in OSMF.<sup>8</sup>

### 2.8. Function of heat shock proteins (HSP) within the pathogenesis of OSMF

HSP47 is a 47 kDa collagen-binding warmness shock protein (HSP), which belongs to the serine protease inhibitor (serpin) superb own family containing a serpin signature collection and is mainly involved in the processing and best control of collagen molecules.<sup>9</sup>

Warmness surprise protein (HSP 47) is a collagen unique molecular chaperone worried inside the processing and/or secretion of procollagen. HSP forty-seven is extensively upregulated in OSMF. Arecoline was observed to elevate HSP 47 m-RNA expression in fibroblasts, in a dose-based way via MEK, PI3K, and COX-2 signal transduction pathways. Cystatin C, a non-glycosylated fundamental protein, is expanded in an expansion of fibrotic diseases. In a comparable way to HSP forty-seven, Cystatin C becomes located to be upregulated both at m-RNA and protein levels inside the disorder. Arecoline is answerable for this enhancement in a dose-dependent way.<sup>10</sup>

### 2.9. Function of primary fibroblast increase issue (bFGF) in the pathogenesis of OSMF

The bFGF might also both without delay stimulating endothelial mobile proliferation or facilitate VEGF-endothelial cell interaction through the modulation of endothelial cell integrin. The expanded bFGF expressivity in endothelial cells alongside fibroblasts in OSF instances was an essential observation, as bFGF potentiates leukocyte recruitment to irritation by way of enhancing endothelial adhesion molecule expression.<sup>11</sup>

That hypoxia performs a position in malignant transformation and progression of OSMF, has identified that HIF-1 $\alpha$  is upregulated at each protein and mRNA tier. alongside the truth that HIF-1 $\alpha$  is a regarded transcription factor prompted through hypoxia, we proposed that hypoxia together with HIF-1 $\alpha$  plays a function in the malignant transformation of OSMF. The opportunities of using HIF-1 $\alpha$  as a marker for malignant transformation have also been mentioned.<sup>12</sup>

The development of fibrosis will increase the hazard of improvement of epithelial dysplasia. accelerated fibrosis of the connective tissue reasons a discount of vascularity ensuing in hypoxia and subsequent overexpression of HIF-1 $\alpha$ .<sup>13</sup>

## 3. Treatment

### 3.1. Dietary support

Supplementary diets administered to OSMF patients are in particular for high protein and energy and for diet B complex and different nutrients and minerals. These are typically employed in combination with different more specific therapeutic dealers like ingestion of iodinated salt and/or local packages.<sup>14</sup>

### 3.2. Immunomodulatory medications

Local and systemic utility of glucocorticoids and placental extract are generally used. Via opposing the movement of soluble factors launched by using sensitized lymphocytes following activation by way of precise antigens,

glucocorticoids act as immunosuppressive markers. those additionally prevent or suppress inflammatory reactions, thereby preventing fibrosis by reducing fibroblastic proliferation and deposition of collagen.<sup>15</sup>

### 3.3. Physiotherapy

Physiotherapeutic measures including forceful mouth beginning and warmth remedy had been attempted. The previous has been nearly discarded due to the terrible results and the fact that it could intensify the fibrosis. warmth has been normally used and the effects have been described as first-rate. It can be in the form of hot rinses, lukewarm water, or selective deep heating remedies like quick-wave and microwave diathermy. The latter avoids the inadvertent heating of the superficial facial tissues like pores skin and adipose tissue.<sup>15</sup>

### 3.4. Nearby drug delivery

Nearby injections of dexamethasone, hyaluronidase, and placental extract were tried. In vitro, collagen from sufferers with OSMF, in evaluation to ordinary collagen, is attacked hastily by means of hyaluronidase. Chymotrypsin, an endopeptidase, hydrolyses the ester and peptide bonds, hence acting as a proteolytic anti-inflammatory agent.<sup>13</sup> The other movements of the placental extract are an anti-inflammatory and significant analgesic impact, boom in blood circulation and tissue vascularity, arrest of tissue boom stagnation, metabolic degenerative situations, and reduced immunity response factors.<sup>14</sup>

## 4. Discussion

Oral Submucous Fibrosis (OSMF) is a chronic and revolutionary disorder that impacts the oral mucosa, causing it to stiffen and making it hard to open the mouth. This condition notably impairs the exceptional of lifestyles affected people. OSMF has an unpredictable reason, and its progression varies from man or woman to man or woman, making remedy outcomes unsure. If detected at an early degree, quitting the habit that would have caused OSMF may be enough to control the circumstance.

They are characterized by the revolutionary stiffening of the mucosa within the mouth, leading to problems in commencing the mouth and a widespread decline within the patient's exceptional life. In summary, OSMF is a modern oral circumstance with an unsure etiology, variable remedy outcomes, and higher potentialities for control whilst detected in its early stages through addressing the underlying causative behavior.

## 5. Summary

Subsequently, thinking about the chronicity of this disorder, OSMF is called a revolutionary disease this is characterised clinically by means of the stiffening of an in other case

yielding mucosa resulting in problems in establishing the mouth, worsening the nice of lifestyle. Because of the unpredictable etiology, immune response/immune reputation of character sufferers, and modality of treatment, no complete success may be assured for OSMF. If the sickness is detected at a completely early degree, cessation of the habit is sufficient.

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None.


## 7. Conflict of Interest

None.


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## Author biography

Juveria Ahmed, PG Student  <https://orcid.org/0009-0005-2380-4823>

**Abhiney Puri**, Professor  <https://orcid.org/0009-0005-4120-9390>

**Rajat Nangia**, Professor  <https://orcid.org/0000-0002-5017-6325>

**Safiya Bhat**, PG Student  <https://orcid.org/0009-0003-2954-9515>

**Akshita Pasbola**, PG Student  <https://orcid.org/0009-0005-6049-1475>

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