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Oral Submucous Fibrosis- Review

KEYWORDS: premalignant condition, areca nut, surgical management

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ABSTRACT *OSMF is one of the classic "Disease of civilization" with large differences being seen between races, geographic areas and individuals at different levels in both prevalence and the degree to which it transforms into malignancy with continuation of habit with increased frequency and duration. Oral Sub mucous Fibrosis is a premalignant condition that has received considerable attention in past because of its chronic debilitating and resistant nature. It is now strongly believed that there is a definite relation of the condition with the habit of areca nut chewing .The possible precancerous nature of OSMF first was described by Paymaster and later confirmed subsequently by Pindborg. In India, the first mention of this disease can be traced back to the ancient literature of 'Sushruta' as 'Vidari'. It was in 1952, when Joshi from Mumbai described the condition as 'Submucous fibrosis' and Pindborg in 1966 named the condition 'Oral sub mucous fibrosis.' There being no actual treatment for the condition per se the mainstay of*

management is concentrated upon improving the mouth opening and relieving the symptoms by therapeutic and/or surgical means.

This review aims to throw the light on etiology, pathogenesis, various classification system, clinical and histopathological features in various stages of OSMF and different treatment modalities.

Introduction:
Oral submucous fibrosis is an insidious, chronic disease affecting any part of oral cavity and sometimes the pharynx. Occasionally it is preceded by and or associated with vesicle formation and is always associated with a juxtaepithelial inflammatory reaction followed by progressive hyalinization of the lamina propria. [1]

OSMF is indeed one of the classic "Disease of civilization" with large differences being seen between races, geographic areas and individuals at different levels in both prevalence and the degree to which it transforms into malignancy with continuation of habit with increased frequency and duration.

Terminology & Definition
In ancient medicine **Sushruta** described the condition "**Vidari"** under mouth and throat diseases.[2] **Schwartz (1952)** describing the condition in five Indian women in Kenya called it "**Atrophica Idiopathica (tropica) Mucosae Oris[3]". Joshi (1953)** from Bombay described the disease for the first time in India and coined the term **Oral submucous fibrosis[4]. Su.I.Pin (1954)** reported three cases of a similar condition among Chinese from Taipei in Taiwan and designated the condition as **"Idiopathic Scleroderma of Mouth**[5]". **Pindborg and Sirsat (1966)** felt that a more appropriate term for this condition was **"Juxtaepithelial Fibrosis"**. They defined oral submucous fibrosis as an "insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by a fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat[6] ".**WHO [1978]** defined OSMF as a slowly progressive disease in which fibrous bands forms a blanched oral mucosa resulting in severe restriction of movement of the mouth.[7]

Epidemiology
Numerous published reports on OSMF have helped get an informed appraisal of its geographical distribution together with data on its percentage prevalence in different parts of the world. **Schwartz (1952)** described OSMF in five Indian women from Kenya.**Wahi PN, Luthra UK. et al (1966)** reported 104 cases of submucous fibrosis in their histomorphological study that were confirmed histologically.[8]**Mehta FS** (**1972**) based on base line data recorded a prevalence of OSMF to be 0.2% in Gujarat, 0.4% in Kerala, 0.04% in Andhra Pradesh, 0.07% in Bihar and 0.03% in Maharashtra.[9] **Gupta SC and Yadav YC (1978)** reported 30 cases of OSMF from 1974 - 75 March in Gorakhpur U.P India[2]. **George L., Olga B. et al (1981)** reported a case of OSMF in a 67 year old Greek female.[10] **Seedat HA and Van Wyk CW** (**1988**) reported that 5% of the total Indian population in South Africa could be betel nut chewers and 2.3% may develop OSMF.[11] **Chiu CJ** (**2002**) *et al* reported that about five million Indians (0.5% of Indian population) were affected with OSMF. This indicates that the worldwide estimate will be much higher in recent times[12]. **Ranganathan K, Uma D. et al (2004)** reported 185 patients diagnosed as OSMF in Chennai in a hospital based study over a period of 3 years.[13] **Liao PH, Kok SH et al (2005)** reported that about five million Indians (0.8% of Indian population) were affected with OSMF. This indicated that worldwide estimation will be much higher in recent times.[14]

Sharma R et al : (2012) carried out cross sectional study to access the prevalence of OSMF in rural areas of Jaipur Rajasthan and prevalence of OSMF in study population was 231(3.39%).Majority of subjects were males 188 (81.38%) and prevalence of OSMF was maximum in 15 to 29 year age group.[15]

Etiology:
1. Chillies:
The use of chillies (*Capsicum annum* and *Capsicum frutes-*

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cence) has been thought to play an etiological role in oral submucous fibrosis. Capsaicin which is vanillylamide of 8-methyl-6-nonenic acid is the active ingredient of chillies play an etiological role in oral submucous fibrosis.[16] OSMF is found mostly among Indians and other population groups who use chillies. A frequent observation is that OSMF patients are unable to tolerate spicy food containing chillies which form a part of their normal diet before they develop the disease.[17]

2. Areca Nut

Areca nut use is considered to be the most important etiologic factor for OSMF.[17]

Ingredients of Arecanut:

- Ethanolic extracts: Arecoline, arecaidine, guvacine, isoguvacine and guvacholine.
- Arecoline esterase arecaidine, gallotanic acid
- Arecanut polyphenols and tannins like gallic acid, catechin, gallotanic acid, D-catechin (0.4%)
- Dimethyl sulfoxide (11.4% - 26%)
- Arecanut alkaloids (0.15%-0.67%) arecoline, arecolidine.
- **Arecanut specific nitrosamines:**
  - 3-(methyl-nitrosamino) propionitrile
  - 3-(methyl-nitrosamino) propionaldehyde
  - N-nitroguvacoline
  - N-nitroguvacine

Other components comprise fats, carbohydrates, proteins and mineral matter.[17, 18]

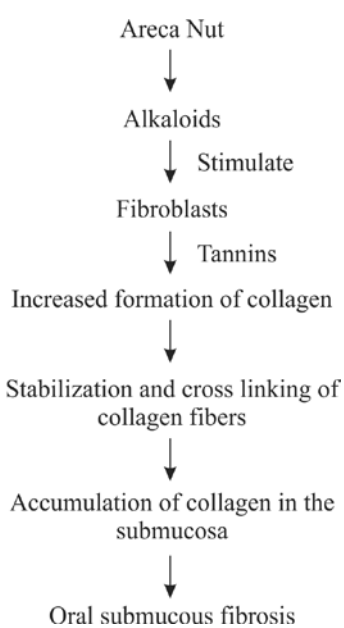


Figure 1: Role of areca alkaloids in OSMF

Ref: Gupta MK, Mhaske S, Ragavendra R , Imtiyaz. Oral submucous fibrosis - current concepts in etiopathogenesis. People's Journal of Scientific Research 2008 ; 1 : 39-44

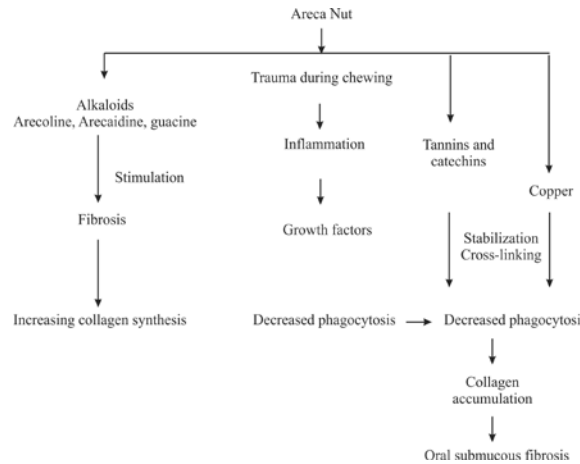


Figure 2: Role of areca nut in OSMF

Ref: Gupta MK, Mhaske S, Ragavendra R, Imtiyaz. Oral submucous fibrosis - current concepts in etiopathogenesis. People's Journal of Scientific Research 2008; 1: 39-44

3. Nutritional Deficiencies

Malnutrition is a major problem for the inhabitants of most countries where OSMF is prevalent. Deficiencies of vitamins and iron have been implicated as being of etiological importance in OSMF. Yet despite these observations the actual role played by these factors remains unclear as these micronutrients may also be deficient in control subjects without OSMF. Obviously these deficiencies also occur in those people who are indigenous to Western countries and who do not have the condition.[19]

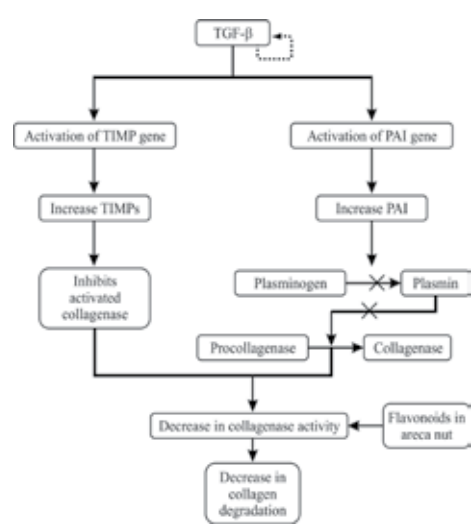
4. Defective Iron Metabolism:

Microcytic hypochromic anemia with high serum iron has been reported in oral submucous fibrosis[15].

5. Immunological Alterations

The reasons for investigating an autoimmune basis included slight female predilection and occurrence in the middle aged patients the presence of circulating immune complexes and the detection of various autoantibodies in patient's sera.[20]

ETIO-PATHOGENESIS OF ORAL SUBMUCOUS FIBROSIS



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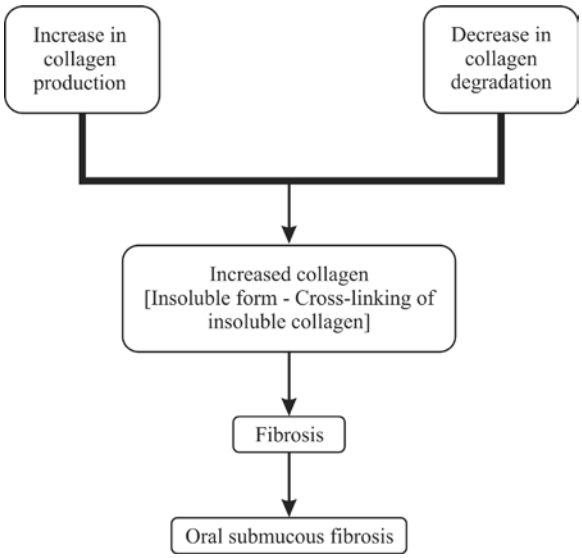

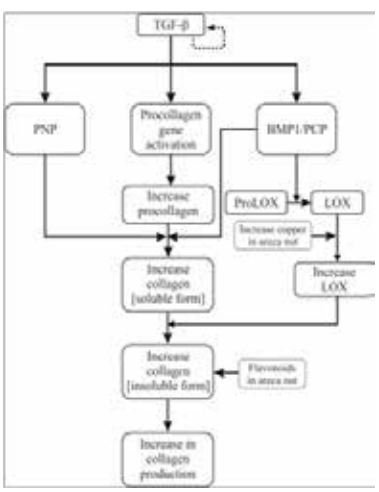

Figure 3: Etio-Pathogenesis of Oral Submucous Fibrosis
TGF-β= transforming growth factor TIMP gene = tissue inhibitor of matrix metalloproteinase gene PAI = plasminogen activator inhibitor PCP = procollagen C-proteinase BMP1=bone morphogenetic protein1 PNP = procollagen N-proteinase LOX = lysyl oxidase.

Ref: Rajalalitha P and Vali S. Molecular pathogenesis of oral submucous fibrosis – a collagen metabolic disorder. J Oral Pathol Med 2005; 34: 321–8.

Classification of OSMF:

1. Classification systems based on clinical features are

A. Pindborg J.J (1989)

B. Lai DR *et al* (1995)

C. Ranganathan K *et al* (2001) and

D. Rajendran R (2003).

2. Classification systems based on histopathological features are

A. Pindborg J.J *et al* (1966) and

B. Utsunomiya H *et al* (2005).

3. Classification systems based on clinical and histopathological features are

A. Khanna JN *et al* (1995).

CLINICAL FEATURES:

The onset of OSMF is insidious, over two to five years.

symptoms and signs reported by patients were

a) Burning sensation exacerbated by spicy or acidic foods.

b) Pain – often referred to temporal region.

c) Increased (early) or decreased (later) salivation

d) Reduced mouth opening

e) Difficulties with mastication phonation and / or deglutition and hearing loss.

f) Vesiculation or ulceration of the oral mucosa

On visual and digital examination of mouth

a) 'Blanching' of mucosa

b) 'Leathery' mucosa; thickened firm tissue with a wrinkled surface.

c) 'Bands' within mucosa; typically 2-4 mm wide. These run vertically in the cheeks and transversely in the lips and soft palate.

d) 'Woody' changes to mucosa or tongue. This is a combination of leathery and bands producing broad areas of inelastic tissue with a wrinkled atrophic surface.[21]

HISTOPATHOLOGICAL FEATURES

1. **Very early stage:** Histopathology revealed finely fibrillar collagen dispersed with marked edema, plump young fibroblasts containing abundant cytoplasm, dilated and congested blood vessels and inflammatory cells consisting primarily of polymorphonuclear leukocytes with occasional eosinophils.

2. Early stage: Histopathology revealed juxtaepithelial area showing early hyalinization collagen still in separate thick bundles, moderate numbers of plump young fibroblasts, dilated and congested blood vessels and inflammatory cells consisting primarily of lymphocytes, eosinophils and occasional plasma cells.

3. Moderately Advanced stage: Histopathology revealed moderately hyalinized collagen slight residual edema separating thickened collagen bundles, less marked fibroblastic response either normal or compressed blood vessels and inflammatory exudate consisting of lymphocytes and plasma cells.

4. Advanced stage: Histopathology revealed completely hyalinized collagen collagen as smooth sheets with no separate bundles, edema is absent, hyalinized area devoid of fibroblasts, completely obliterated or narrowed blood vessels and inflammatory cells consisting of lymphocytes and plasma cells[19].

MALIGNANT POTENTIAL

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The precancerous nature of OSMF was first described by **Paymaster** (**1956**) when he observed slow growing OSCC in one third of the patients with the disease.

Pindborg JJ *et al* (**1968**) supported the hypothesis that OSMF is a precancerous condition.[23]

Pindborg JJ (**1972**) put forward five criteria to prove that the disease is precancerous. They included

a. High occurrence of OSMF in oral cancer patients

b. Higher incidence of OSCC in patients with OSMF

c. Histological diagnosis of cancer without any clinical suspicion in OSMF

d. High frequency of epithelial dysplasia and

e. Higher prevalence of leukoplakia among OSMF cases.[24]

However, according to the current awareness of the disease and some refined criteria for grading dysplasia, it is reasonable to assume that the prevalence of dysplasia is more towards the midway of the reported range. Malignant transformation rate of OSMF was found to be in the range of 7–13% [15].

The hypothesis that dense fibrosis and less vascularity of the corium, in the presence of an altered cytokine activity creates a unique environment for carcinogens from both tobacco and areca nut to act on the epithelium is widely being accepted. It could be assumed that carcinogens from areca nut accumulate over a long period of time either on or immediately below the epithelium allowing the carcinogens to act for a longer duration before it diffuses into deeper tissues.

TREATMENT

Rajendran R (**1994**) suggested that 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 probably slow the progress of the disease. The following strategies have been proposed.[25]

1. Nutritional support
2. Immunomodulatory drugs
3. Physiotherapy
4. Local drug delivery
5. Combined therapy and
6. Surgical management

Conclusion:

OSMF is now accepted globally as an Indian disease, having highest malignant potential than any other oral premalignant lesions. Various available data suggests that the main causative agents for OSF are the constituents of areca nut, mainly arecoline, whilst tannin may have a synergistic role. Arecoline will interfere with the molecular processes of deposition and/or degradation of extracellular matrix molecules such as collagen. The understanding of the exact role of alkaloids and other etiological agents with respect to pathogenesis will help the management and minimize the blind clinical trials and treatment modalities

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