ORAL SUBMUCOUS FIBROSIS: A REVIEW ARTICLE ON ETIOPATHOGENESIS

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ABSTRACT

Areca quid chewing related oral mucosal lesions are potential hazard to a large population worldwide. Commercially freeze dried products such as pan masala, guthka and mawa have high concentration of areca nut per chew and appear to cause OSMF more rapidly than by self prepared conventional betel quid that contain smaller amounts of areca nut. The basic constituent of areca nut is either raw or dried or boiled or baked. Diverse agents including lime, tobacco, catechu, cloves, saffron and leaf of piper betel leaves may form a part of formulation. Many of the undesirable aspects of areca nut have been attributed to arecoline. These chemical appear to interfere with the molecular processes of deposition and or degradation of extracellular matrix molecules such as collagen, causing imbalance in the normal process. The most likely events that take place with regards to the above imbalance may be reduced phagocytosis of collagen by fibroblasts, up or down regulation of copper dependent enzyme lysyl oxidase, matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases . It has been postulated that areca nut may also induce the development of the disease by increased levels of cytokines in the lamina propria. Current evidence implicates collagen related genes in susceptibility and pathogenesis of OSMF. The individual mechanisms operating at various stages of the disease- initial, intermediate and advanced–need further study in order to propose appropriate therapeutic interventions.

KEYWORDS

Areca-nut, matrix metalloproteinases, oral sub mucous fibrosis.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a disease due to a chronic, insidious change in fibro-elasticity, characterized by burning sensation in the oral cavity, blanching, and stiffening of the oral mucosa and oro-pharynx leading to trismus and inability to open the mouth. The symptoms and signs depend on the progression of the lesions and number of affected sites.[1] It is characterized by loss of mucosal elasticity and excessive fibrosis and is always associated with juxta epithelial inflammation and progressive hyalinization of lamina propria.[2,3,4] It was described by Schwartz in 1952 as a fibrosing condition of the mouth in 5 Indian women from Kenya for which he coined the term. "*Atrophica idiopathica tropica mucosae oris*".[5]

Recent epidemiological data indicates that OSMF has been largely reported among subjects living in the Indian Subcontinent, neighboring Asian Countries and among the Asian immigrants living in South Africa, Malaysia and UK. It is found in Asians or Asians settled in other countries. So an ethnic basis for the disease was suggested.[6]

Oral submucous fibrosis (OSMF) is a premalignant condition mainly associated with the practice of chewing betel quid containing areca nut, a habit common among South Asian people. It is characterized by inflammation, increased deposition of submucosal collagen and formation of fibrotic bands in the oral and paraoral tissues, which increasingly limit mouth opening.[7]

OSMF is a well-recognized potentially malignant condition in the oral cavity, & the transformation rate as high as 7.6% over a period of ten year have been reported from india.[8]

Study done by Kumar et al reveals increased frequency of gutkha usage was directly associated with malignant transformations in oral submucous fibrosis.[9]

Various hypotheses were put forward which suggest a multifactorial origin for the etiology of OSMF. The etiological factors include local irritants such as chili consumption, areca nut chewing, tobacco smoking and chewing. Systemic factors include anemia (iron deficiency), vitamin deficiencies (B-complex and folate) together with the malnourished state (protein deficiency), genetic predisposition to the disease and autoimmunity.[7]

Currently areca nut use is considered to be most important etiological factor in pathogenesis OSMF. The formulation in which areca is consumed varies according to geographical location and often associated with cultural and religious practices. The basic constituent of areca nut is either raw or dried or boiled or baked. Diverse agents including lime, tobacco, catechu, cloves, saffaron, and leaf of piper betel leaves may form a part of formulation.[10]

The aim of the present review is to understand the etiology and pathogenesis of OSMF with special emphasis on areca nut & its constituents.

ETIOPATHOGENESIS

OSMF represents a failed wound-healing process of the oral mucosa after chronic, sustained injury.[11] Etiology of Oral Submucous fibrosis is obscure, but several factors were put forward to suggest a multifactorial origin for this condition. It has been suggested that consumption of chillies, nutritional deficiency, chewing of areca nut, genetic susceptibility, altered salivary constituents, and autoimmunity and collagen disorders may be involved in the pathogenesis of this condition.[10]

Currently areca nut use is considered to be the most important etiological factor in OSMF. This observation has been made in case reports, case control studies, cross sectional studies and interventional studies.[11] In the study done by Vanaja Reddy, gutkha and other areca nut product users like mawa, tobacco when compared to plain panmasala users showed a significant occurrence of OSMF in the severity of the condition.[12] The reason attributes to the fact that the commercially available products as above are concentrated, freeze dried and have higher dry weight concentration of pathology causing irritants in comparison to the traditionally prepared home made products like panmasala. Another factor supporting this could be the antioxidant capabilities of pan leaf which is known to be rich in beta-carotene, which has the capacity to quench free radicals that are mutagenic which counteracts the different pathology causing irritants. [13]

It is apparent that fibrosis and hyalinization of subepithelial tissues account for most of the clinical features encountered in this condition. Moreover, substantial amount of research on elucidating the etiology and pathogenesis appear to have been focused on changes in the extracellular matrix (ECM). It is logical to hypothesize that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in the development of the disease. There are numerous biological pathways involved in the above processes and, it is likely that the normal regulatory mechanisms are either down regulated or up regulated at different stages of the disease.[14] Not a single case of OSMF was found without any chewing habits in a study conducted by Shah et al.[15] This indicates Pan Masala chewing as one of the important risk factor for developing OSMF.

Areca nut

It is the endosperm of the fruit of Areca catechu. It is orange – yellow in color. Areca nut for chewing is obtained by separating the seed from its pericarp. It is consumed in various ways. It is used fresh or dried and maybe cured before use by boiling, baking or roasting. In India alone 38 different combination of areca nut with tobacco have been documented. The number of patients with a paanmasala chewing habit (68.0%) was higher than the number of patients with betel nut (17.4%) or betel quid chewing habits (14.6%).[15]

The major areca nut alkaloids are arecoline, arecadine, arecolidine, guyacoline and guacine.[9] Important flavonoid components in areca nut are tannins and catechins. These alkaloids undergo nitration and give rise to N-nitrosamine which might have cytotoxic effect on cells.[16]

Molecular pathogenesis:

Of all of the growth factors, none has been found to have the diversity of effects on extracellular matrix (ECM) ascribed to transforming growth factor-β (TGF-β). This peptide plays a critical role not only in synthesis and degradation of ECM but also in response of cells to ECM mediated through integrin receptors; moreover, specific components of the ECM, in turn, can both deliver TGF- β and regulate its activity.[4,15]

Over a period of time, due to persistent habit, chronic inflammation sets in at the site. Initial irritation leads to further atrophy and ulceration of the mucosa. It can thus be considered that induction of oral mucosal inflammation by betel quid ingredients is a critical event in the pathogenesis of OSMF. Cytokines like interlukin-6 (IL-6), tumor necrosis factor (TNF), interferon-α(INF-α) etc. and growth factors like TGF-β are synthesized at the site of inflammation. TGF-β1 is a key regulator of extra cellular matrix (ECM) assembly and remodeling. The action of TGF-β on the genes implicated in the formation and degradation of the ECM is mostly exerted at the transcriptional level through ill defined intracellular pathways. TGF-β increases the collagen production and decreases the collagen degradation.

Collagen production pathway

The three main events that are modulated by TGF-β, which

favors collagen production, are:

1. Activation of procollagen genes

2. Elevation of procollagen protienases levels

- procollagen C-protienase (PCP)/bone morphogenic protein 1 (BMP1) and
- procollagen N-protienase (PNP)

3. Up-regulation of lysyl oxidase (LOX) activity.

Collagen degradation pathway

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

1. Activation of tissue inhibitor of matrix metalloproteinase gene (TIMPs).

2. Activation of plasminogen activator inhibitor gene (PAI).[17]

Increased collagen synthesis or reduced collagen degradation serves as possible mechanisms in the development of the disease. There are numerous biological pathways involved in the above processes and, it is likely that the normal regulatory mechanisms are either down regulated or up regulated at different stages of the disease. Among the chemical constituents, alkaloids from areca nut are the most important biologically whilst tannin may have a synergistic role. These chemicals appear to interfere with the molecular processes of deposition and/or degradation of extracellular matrix molecules such as collagen. In vitro studies on human fibroblasts using areca extracts or chemically purified arecoline support the theory of fibroblastic proliferation and increased collagen formation that is also demonstrable histologically in human OSMF tissues.[13] It has been postulated that areca nut may also induce the development of the disease by increased levels of cytokines in the lamina propria. Current evidence implicates collagen-related genes in the susceptibility and pathogenesis of OSMF.[18]

This is further aggravated by the auto regulatory process of TGF-β, which is the main trigger for both the increased collagen production and decreased collagen degradation pathways.[17]

It is known that OSMF is associated with inflammatory changes in at least some stages of the disease. Prostaglandin is one of the main inflammatory mediators and its production is controlled by various enzymes such as cyclo-oxygenase (COX). Biopsies from buccal mucosa of OSMF cases and from controls were stained for COX-2 by immune histochemistry and revealed that there was increased expression of the enzyme in moderate fibrosis and this disappeared in advanced fibrosis.[14]

Role of Heat shock proteins (HSP) in pathogenesis of OSMF

HSP47, is a 47 kDa collagen-binding heat shock protein (HSP), which belongs to the serine protease inhibitor (serpin) super family containing a serpin signature sequence. HSP47 is known as a molecular chaperone that is specifically involved in the processing and quality control of collagen molecules. It was found that arecoline is capable of stimulating HSP47 mRNA expression in human buccal mucosa fibroblast (BMFs). HSP47 plays an important role in the synthesis, processing, and assembly of various collagens. Previously, their data have shown that arecoline could enhance collagen synthesis in human gingival fibroblasts.[3] Similarly, study by Shung Fa found that HSP47 mRNA was upregulated by arecoline in human BMFs. Thus, authors propose that the accumulation of collagen in oral mucosal connective tissue may be caused by a simultaneous effect on HSP47 by areca quid chewing.[14]

Role of basic fibrobalstic growth factor (bFGF) in pathogenesis of OSF

Basic fibroblasts growth factor (bFGF) may either directly stimulate endothelial cell proliferation or facilitate VEGF–endothelial cell interaction through the modulation of endothelial cell integrin or VEGF-receptor expression.[5] The increased bFGF expressivity in endothelial cells along with fibroblasts in OSMF cases was an important observation, as bFGF potentiates leukocyte recruitment to inflammation by enhancing endothelial adhesion molecule expression. The endothelial cell and fibroblast dysfunction may be linked through the paracrine activity of soluble endothelial cell products.[20] Mast cells which are found in the early stages of OSMF are indicated to be a primary source of heparin and may serve as a significant source for heparin binding growth factor, the bFGF, in disease processes.[21] The altered stromal distribution of bFGF in OSMF could be because of lower stromal cell concentration and aberrant extracellular deposition of cytokine.[22]

Recently, the direct effect of bFGF-1 and TGF- β, on fibroblast proliferation and collagen synthesis using cultured oral fibroblasts have shown opposing effects on growth, differentiation and extracellular matrix accumulation. While bFGF was autorepressive and catabolic, TGFb has shown to be autoinductive and anabolic, thus representing a part of feedback mechanism controlling stromal growth. However, when bFGF and TGF β, were associated, the anabolic effects prevailed.[12] Contrary to this effect, bFGF was found to be the most potent growth factor in increasing proliferation, glycosaminoglycans synthesis and promoting collagen synthesis in temporomandibular joint disc (TMJ) cells.[23] Additional studies to test the effect of bFGF and TGF-b alone and in combination on cultured fibroblasts from OSMF tissues may prove beneficial, as these studies may provide a greater insight into its pathogenesis and offer novel options for therapeutic intervention.

CONCLUSION

Evidences suggests that OSMF is multifactorial, with certain effects on specific subpopulations of fibroblasts, genetic predisposition and molecular mechanisms (Cytokines and

Growth factors), which could render the oral mucosa more suspectible to chronic inflammatory changes on exposure to carcinogens. However, the relationship between arecanut and OSMF is well established from epidemiological studies. The chemical constituents of arecanut have been identified as arecoline, arecaidine, guvacine, guvacoline, catachins and tannin in biochemical studies. These chemical constituents of betel nut can stimulate fibroblast proliferation leading to collagen synthesis. Apart from this, these extracts also have the capability to stabilize the collagen fibrils and make it resistant to enzymatic degradation. Arecanut contains a high copper content compared to commonly eaten nuts which is released in the mouth while chewing. Lysyl oxidase, an extracellular copper enzyme is secreted by fibroblasts and initiates post-transitional modification of collagen fibers rendering them resistant to the action of collagenases.

Molecular pathogenesis suggests the role of growth factors such as transforming growth factor (TGF-b), connective tissue growth factor (CTGF) and basic fibroblastic growth factor (b-FGF). TGF-b may play an important role in inducing fibrotic tissue formation, while connective tissue growth factor (CTGF) is important in maintaining fibrosis. Arecoline stimulates CTGF production in buccal mucosal fibroblasts (BMF). b-FGF may directly stimulate endothelial cell proliferation & modulate fibroblast properties independently. Further work is required to establish the effect of bFGF and TGF-b alone and in combination on cultured fibroblasts from the lesion.

In conclusion, additional studies are required to establish the exact the role of betel nut and its constituents in the pathogenesis of OSMF which may prove beneficial in providing a greater insight into its pathogenesis and therapeutic intervention

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