REVIEW ARTICLE

Current Aspects of Pathogenesis of Oral Submucous Fibrosis (OSMF)

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ABSTRACT

Oral submucous fibrosis (OSMF) is a worldwide accepted chronic premalignant condition with overall prevalence rate in India to be about 0.2% to 0.5 % and prevalence by gender varying from 0.2-2.3% in males and 1.2-4.57% in females. Associated etiological factors of this disease are ingestion of chillies, genetic susceptibility, nutritional deficiencies, altered salivary constituents, autoimmunity and collagen disorders. This article provides an overview of the pathogenesis of this chronic disease.

Keywords: Pathogenesis, OSMF, Precancer lesion

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INTRODUCTION

Many mechanisms have been proposed by many authors but the pathogenesis of Oral submucous fibrosis is not well established. Pathogenesis of this disease is believed to involve juxta-epithelial inflammatory reaction and fibrosis in the oral mucosa, probably due to increased cross-linking of collagen through up-regulation of lysyl oxid - ase activity. Fibrosis, or formation of collagen bundles, results from the effects of areca nut, which increases collagen production and decreases collagen degradation. Thus, OSMF is now considered a collagen metabolic disorder.[1]

PATHOGENESIS

Genotoxic effects can best describe the pathogenesis of oral submucous fibrosis which associated with combination of factors such as genetic alterations and carcinogenic agents such as arecanut and tobacco. Many infectious agents such as candida, viruses (HPV, HIV, HSV) play important role in the pathogenesis.

I. Collagen accumulation

Oral submucous fibrosis occurs due to increased production of collagen by fibroblasts and decreased breakdown leading to accumulation of excessive amount of collagen.

a. Increased Collagen Production: Fibroblasts differentiate into phenotypes that produce more collagen under the influence of arecanut which contains alkaloids arecadine and arecoline. Arecoline gets converted into arecadine which is the active metabolite.[3-6]

b. Stabilization of collagen structure and decreased collagen breakdown: One of the mechanisms that can lead to increased fibrosis is by reduced degradation of collagen by forming a more stable collagen structure. Betel nut contains tannin. Tannin has ability to stabilize collagen by cross-linking it. With the progression of the disease type III collagen is almost completely replaced by type I.

Role of arecanut in oral submucous fibrosis[3, 8]

Some authors studied that it could reflect the clonal selection of a highly fibrogenic cell population in the altered tissue under the influence of local factors such as interleukin-1 from inflammatory cells. This leads to accumulation of collagen and decrease in phagocytosis in oral mucosa. Glycogen consumption is physio-

logically associated with cellular activity of muscle fibres. Over activity of muscles occurs in

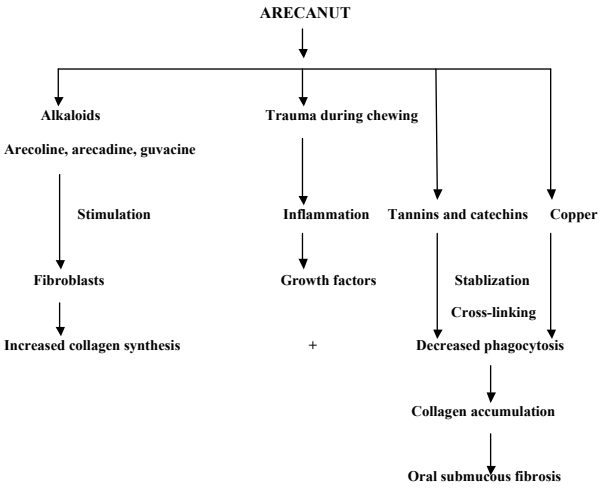

Figure-1: Role of arecanut in oral submucous fibrosis [3, 8]

excessive glycogen consumption, leading to its depletion. I. This increased muscle activity along with diminished blood supply and connective tissue changes leads to muscle degeneration and fibrosis.[3]

II.Increased expression of fibrogenic cytokines

Cytokines play a significant role in regulation of fibroblast , such as proliferation, migration and matrix synthesis, and it is the balance of these mediators that is likely to play a significant role in regulation of initiation and progression of scarring in any fibrotic disease.[9]

Some authors have described increased levels of pro-inflammatory cytokines and reduced anti-fibrotic interferon gamma in patients with Oral submucous fibrosis (OSMF), which may be central to the pathogenesis of OSMF.[10]

The most important finding in the various studies was the demonstration of increased expression of fibrogenic cytokines namely TGFβ-1, PDGF and bFGF in OSMF tissues compared to normal. These observations may suggest that the disease process in OSMF may be an altered version of wound healing as recent findings show that the expression of various ECM molecules are similar to those seen in maturation of granulation tissue.[7]

III Genetic polymorphisms predisposing to OSMF

Polymorphisms of the genes coding for TNF-α has been reported as a significant risk factor for OSMF. TNF-α is known to stimulate fibroblastic proliferation in vitro. Evidence suggest that collagen related genes are altered due to ingredients in the quid. The genes COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 have been identified as definite TGF-α targets and induced in fibroblasts at early stages of the disease. The transcriptional activation of these procollagen genes by TGF-β suggests that it may contribute to increased collagen levels in OSMF.[3,11,12] Areca nut chewing and/or smoking in OSMF and oral cancer cases may play a role in the p53 over expression.[13]

MOLECULAR PATHOGENESIS

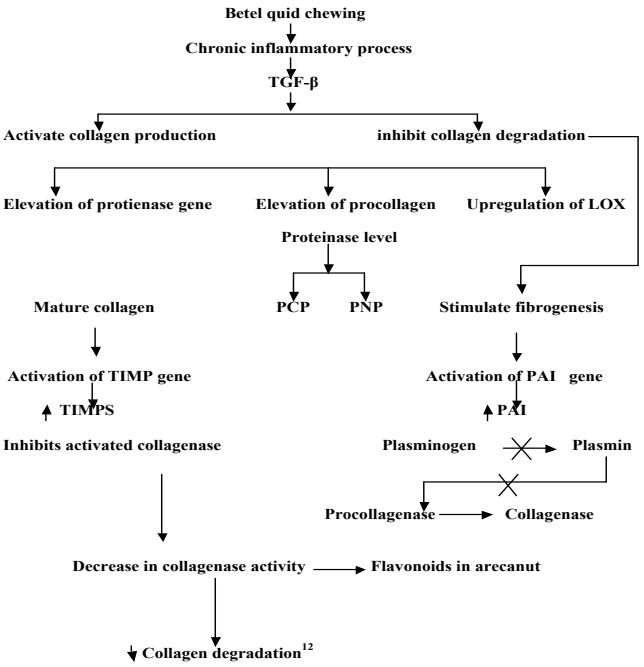

Figure-2: Molecular pathogenesis of OSMF

CONCLUSION

Various research work suggested that the main causative agents for OSMF are the constituents of arecanut, mainly arecoline, while tannin play a synergistic role in this disease. Arecoline will interfere with the molecular processes of

deposition and/or degradation of extracellular matrix molecules such as collagen. Due to this interference, phagocytic capacity of fibroblast is reduced, because of up or down regulation of key enzymes such as lysyl oxidase and alteration inexpression of various ECM molecules. This process may also be influenced by decreases productin of anti-fibrotic cytokines, increased secretion of inflammatory cytokines, and growth factors. Therefore the above mechanisms may explain the induction, stabilization and progression of fibrosis in OSMF, Although the involvement of HLA and genetic predisposition has been reported, specific haplotypes have not been determined.

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