ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

A Review

ETIOPATHOGENESIS OF ORAL SUBMUCOUS FIBROSIS: A CONCISE UPDATE

Authors:

Sanjeev Tomar[1], Amit B. Lall[1], Mayank Singhal[1], Upma Tomar[2], Anupam Bhardwaj[1], Priyanka Takhellambam[1]

[1]Dept. of Oral and Maxillofacial Surgery, Santosh Dental College and Hospital, Santosh Deemed to be University, Ghaziabad, NCR Delhi.

[2]Dept. of Oral and Maxillofacial Pathology & Microbiology, Inderprastha Dental College and Hospital, Ghaziabad, NCR Delhi.

Address for Correspondence: Dr. Sanjeev Tomar,
Associate Professor, Dept. of Oral and Maxillofacial Surgery, Santosh Dental College and Hospital, Santosh Deemed to be University, Ghaziabad, NCR Delhi.

ABSTRACT- Oral Submucous Fibrosis is a premalignant condition with a greater preponderance in countries such as India. Epithelial atrophy of the oral mucosa, juxta-epithelial inflammation, and chronic fibrosis of the lamina propria, resulting in the peculiar clinical presentations of progressive trismus, dysphagia, burning sensation and intolerance to spicy foods, blanched, opaque leather-like mucosa, thick fibrosed bands on the buccal mucosa in the retromolar area and at pterygomandibular raphe of this disease. Although many factors are responsible for the occurrence of OSMF, but multiple types of research have proven that areca nut is the primary causative factor in OSMF. It is an enigma to Oral & Maxillofacial Surgeons because of its chronic, progressive and higher malignant transformation. The present study was undertaken to assess the correlation between different factors and its course of disease progression as OSMF.

KEYWORDS- Oral Submucous Fibrosis, Areca Nut, Malignant Transformation, Trismus

INTRODUCTION-

Oral submucous fibrosis (OSMF) is an oral disease. It is considered a pre-cancerous condition.[1] In ancient times Sushruta, described a similar condition called, "Vidari," the features of which simulate OSMF. Schwartz gave a detailed description of this condition in 1952 and named as "atrophia idiopathica (tropica) mucosae oris" which was later on called OSMF by Joshi in 1953.[2,3] According to Pindborg and Sirsat, OSMF is characterized by a juxtaepithelial inflammatory reaction followed by fibroelastic change in the lamina propria and associated epithelial atrophy.[1] Due to which restricted mouth opening, resulting as trismus which results in restriction of food consumption leads to difficulty in maintaining

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

overall health, as well as hampers the ability to speak. The fibroelastic bands are evident in the almost entire subepithelial layer, resulting in dense fibrous bands developing in the mouth. This condition is also called juxta-epithelial fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, submucous fibrosis of the palate and pillars, sclerosing stomatitis, and diffuse OSMF.[3]

Most cases are reported of this condition are reported in 2^{nd} – 4^{th} decade with male predilection because of dietary habits.[3] Usually it takes 2–5 years of duration to recognize this disease in oral cavity.

EPIDEMIOLOGY

Southeast Asian countries are affected the most due to dietary culture and habits including India, Taiwan, China, Bangladesh, Malaysia, Singapore, Thailand and Sri Lanka. However other Asian countries are also affected such as Saudi Arabia but the incidence rate is lower.[4] Preponderance of OSMF in India is about 0.2%–0.5%. This increased Preponderance is due to the increased use and popularity of commercially prepared - gutkha, pan masala, flavored supari, etc. due to cultural and religious reasons.[5]

CLINICAL PRESENTATION

Peculiar symptom of OSMF is a severe burning sensation in the oral cavity after ingesting spicy foods. The patient also experienced other symptoms including dry mouth, pain, taste disorders, restricted tongue mobility, trismus, dysphagia, and altered tone. This disease contributes significantly to mortality because of its high malignant transformation rate (1.5–15%).[6] Average malignant transformation rate of OSMF was found tobe 7.6%.[4]

ETIOPATHOGENESIS

A number of factors are responsible for the etiopathogenesis of this disease. These factors elicit the disease process by causing a juxtaepithelial inflammatory cell infiltrate in the oral mucosa. Etiological Factors include areca nut chewing, ingestion of chilies, genetic and immunologic processes, nutritional deficiencies, and other factors. The chewing of betel quid (BQ) (containing areca nut, tobacco, slaked lime or other species) has been confirmed as the prime cause of occurrence of OSMF. The role of betel-quid is also supported by the epidemiological evidence as well as from its confirmed histopathological effects on fibroblasts and keratinocytes.[5, 6]

INITIATION OF OSMF

OSMF is a collagen-metabolic disturbance that occurs as a result of the consumption of areca nuts. Collagen-fibres, is the main structural component of the connective tissues and it is an important element in each tissue for its proper tissue integrity. To maintain metabolic-equilibrium proper degradation, as well as production of collagen is necessary, but because of the effect of areca-nut decreased degradation of collagen due to increased cross-linking of the fibres and reduced collagenase activity are found in OSF mucosa compared to the normal oral mucosa.[1]

ROLE OF ARECA-NUT

The areca nut (betel nut) component of BQ plays a major role in the pathogenesis of OSMF. Areca-nut, catechu with slaked lime wrapped in betel-leaf along with a few taste-enhancers

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

forms Betel-Quid. People of the lower middle class used to chew betel as it causes euphoria, increases salivation, satisfies hunger, relieves tooth pain, etc. Also, people of other classes consumed betel quid because of religious and cultural habits. Areca Nut plays an important role in the initiation of Chemical as well as Mechanical Irritation. Areca nut has an alkaloid called arecoline which exerts an effect as an abnormal increase in collagen production (Figure 1).[1]

MECHANICAL IRRITATION INDUCED BY ARECA NUT

The chewing habit differs in different individuals, but mostly habitual betel-quid chewers place it in the buccal vestibule, without chewing for about 15 min to an hour and usually intake of betel-quid is five to six times a day. Hence there is constant contact between the betel-quid and oral mucosa. The BQ is seeped, absorbed and ultimately undergoes metabolism. These alkaloids and flavonoids cause irritations. BQ constituents and their metabolites, the coarse fibers of areca nut results in mechanical irritation to the oral mucosa. So because of this microtrauma produced by the friction of coarse fibers of areca nut, it also facilitates the diffusion of BQ alkaloids and flavonoids into the subepithelial connective tissue.

CHEMICAL IRRITATION INDUCED BY ARECA NUT

Because of mechanical irritation, several alkaloids seep in the sub-epithelial layer. Due to persistent habit, after a period of time, these alkaloids cause, chronic inflammation at the site. Thus, it can be considered that, induction of oral mucosal inflammation is induced by initial mechanical inflammation by BQ ingredients. It is confirmed to be a critical event in the pathogenesis of OSMF. As a result, Cytokines like Interleukin 6, Tumor Necrosis Factor (TNF), Interferon A, etc. (1) and growth factors like TGF-b are synthesized at the site of inflammation. Further these two mechanism initiates molecular events.

The molecular events are discussed in this review under two main sections: collagen production pathway and collagen degradation pathway, as regulated by TGF-b and the flavonoids present in areca nut.

COLLAGEN PRODUCTION PATHWAY

Collagen production is initiated and regulated by the Transforming growth factor. The role of TGF-b in the formation of collagen are as follows:

(1) Activation of procollagen genes.

(2) Elevation of procollagen proteinases levels: Procollagen C-Proteinase (PCP) and Procollagen N-Proteinase (PNP)

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

TGF-b's role as a growth factor is to convert pro-collagen into collagen with the help of activation of the procollagen genes. It also increases the secretion of PCP and PNP, both of which are essential for the conversion of pro-collagen to collagen fibrils. Insoluble forms of collagen fibres are increased because of cross-linking between these collagen-fibres, which

ISSN PRINT 2319 1775 Online 2320 7876

Review paper © 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

leads to OSMF. In this whole activity, an enzyme LOX plays an important role, which activates by copper content, which again present in betel quid, as a result, OSMF occurs.

{**Abbreviation:** Pro-LOX (Pro-Lysyl Oxidase), LOX (Lysyl Oxidase), PNP (Pro-Collagen N-Proteinase), PCP (Pro-Collagen, C–Proteinase), BMP1 (Bone Morphogenetic Protein 1). }

COLLAGEN DEGRADATION PATHWAY

On the other side, there are two main events initiated by TGF-b, which reduces collagen degradation. These are-

(i) Activation of tissue inhibitor of matrix metalloproteinase gene (TIMPs)

(ii) Activation of plasminogen activator inhibitor (PAI) gene.

TGF-b plays a key role in collagen degradation by activating the genes for TIMPs; thereby more TIMP is formation occurs. TIMPs inhibit the activation of the collagenase enzyme which is required for the degradation of collagen. So, collagen degradation decreases. Activation for the genes for PAI also occurs, which is an inhibitor of plasminogen activator, hence there is no plasmin formation. Plasmin is necessary for the conversion of pro collagenase to the active form of collagenase and lack of plasmin results in the absence of active collagenase, which ultimately increase the amount of collagen.

CONCLUSION

As described in this review, OSMF can be regarded as a disease of collagen-metabolic disorder. Overall increased collagen production and decreased collagen degradation results in increased collagen deposition in the oral tissue, leading to fibrosis (Figure 2).

The autoregulatory mechanism of TGF-b, which is the primary catalyst for both the increased collagen formation and the reduced degradation pathways, exacerbates this fibrosis further. Along with a decline in collagen degradation, there is an increase in collagen synthesis and cross-linking (insoluble form). This produces an increased collagen deposition in the subepithelial connective tissue layer of the oral mucosa leading to OSMF. Understanding of molecular events helps in better therapeutic intervention of the disease. TGF-b is an important cytokine involved. LOX is to be a key enzyme tilting the balance in the collagen metabolism toward fibrosis. As the inflammatory process is the main factor that leads to fibrosis, anti-inflammatory/immuno-modulatory drugs such as colchicines and steroids can be effective. Presently hyaluronidase (that breaks down the components of connective tissue) intralesional injection along with steroids has been used for OSF therapy. Cessation of BQ chewing habit is very important for any of the treatment modalities.

REFERENCES

1. Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis-A collagen metabolic disorder. J Oral Pathol Med 2005;34:321-8.
2. Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y. Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies. Natl J Maxillofac Surg 2017;8:89-94
3. Murthy, V.; Mylonas, P.;Carey, B.; Yogarajah, S.; Farnell, D.;Addison, O.; Cook, REscudier, M.;Diniz-Freitas, M.; Limeres, J.; et al. Malignant Transformation Rate of

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

Oral Submucous Fibrosis: ASystematic Review and Meta-Analysis. J. Clin. Med. **2022**, 11, 1793.

4. Sathe RS, Gharote HP, Nair PP, Hegde KJ, Sood MS, Gangwal PA. Correlation of areca habit, clinical grading, anorexia, and fatique in oral submucous fibrosis. J Dent Res Rev 2015;2:109-12.
5. Yin-Hwa Shih,Tong-Hong Wang,Tzong-Ming Shieh,Yu-Hsin Tseng, Oral Submucous Fibrosis: A Review on Etiopathogenesis, Diagnosis, and TherapyInt. J. Mol. Sci. 2019, 20, 2940
6. Jitesh.S, Santhosh Kumar M.P, Madhulaxmi M. Treatment Modalities:In The Management Of Oral Submucous Fibrosis - An Institutional Study-- Palarch's Journal Of Archaeology Of Egypt/Egyptology 17(7), 483-494.
7. Anagha A Motgi, Mrinal V Shete, Mahesh S Chavan, Nikkhiel N Diwaan,Rashmi Sapkal, Pallavi Channe : Assessment of correlation between clinical staging, functional staging, and histopathological grading of oral submucous fibrosis. J Carcinog. 2021; 20: 16.
8. Arpita Rai, Musarrat Siddiqui, Shama Parveen, Saba Parveen, Abdur Rasheed and Sher Ali. Molecular Pathogenesis of Oral Submucous Fibrosis: A Critical Appraisal *Biomed. & Pharmacol. J*, Vol. 12(4), 2027-2036 (2019)

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

FIGURES:

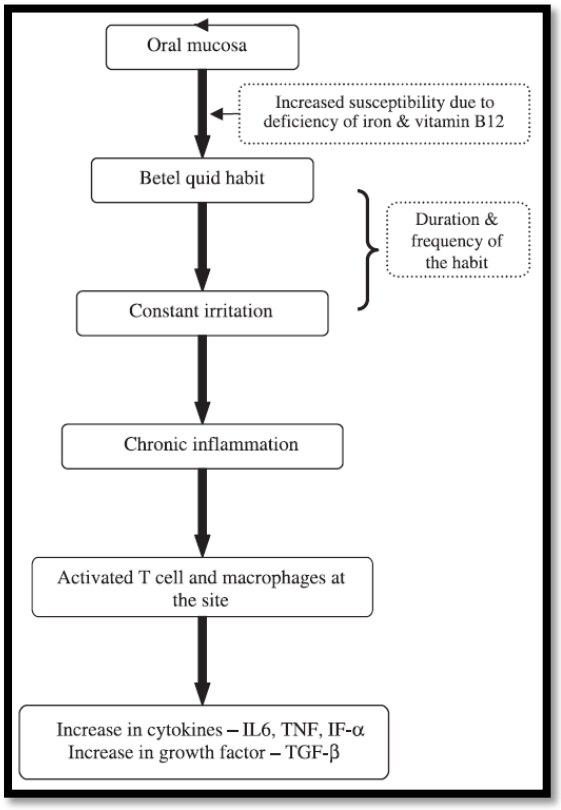

Figure 1: Initial event of pathogenesis of OSMF[1]

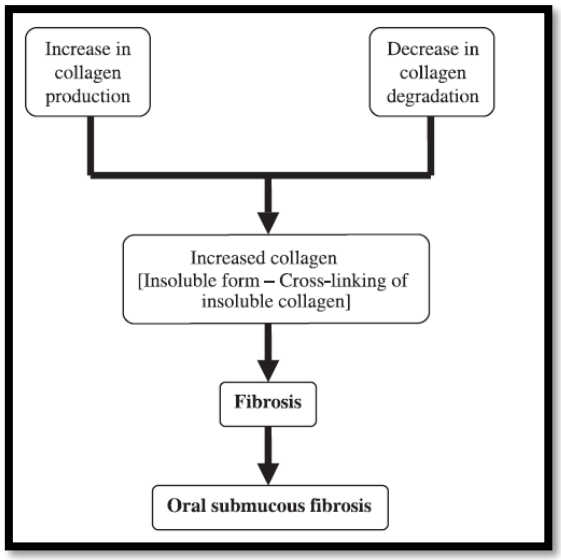

Figure 2: Overall effect of activated TGF-b pathway[1]