UNRAVELING THE PATHOPHYSIOLOGY OF ORAL SUB MUCOUS FIBROSIS: MECHANISMS AND INSIGHTS

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ABSTRACT

Oral Submucous Fibrosis (OSF) is defined by enhancing irreversible fibrosis of the oral mucous membrane, a potentially malignant disorder that results in dysphagia, restricted mouth opening and in an advanced case, the onset of malignancy. Immunological, environmental, and genetic factors all play a part in the complex pathophysiology of OSF . The most well-established risk factor is long-term chewing of areca nuts (betel nuts), which causes an inflammatory response that produces collagen and other extracellular matrix components, ultimately resulting in fibrosis. The pro-inflammatory cytokines such as TNF-α, IL-1 and TGF-β influences the activation of fibroblast and collagen deposition, may be involved, according to molecular research. The disease also progresses as a result of oxidative stress and genetic abnormalities, especially in genes linked to collagen. In a small percentage of cases, this diseased process may eventually result in malignant transformation. The pathophysiology of OSF is reviewed in this paper, with an emphasis on molecular pathways along with prospective therapeutic targets for treatment and prevention.

INTRODUCTION

The persistent, debilitating condition known as oral submucous fibrosis (OSF) mostly affects the oral mucosa and adjacent upper aerodigestive tract areas which is characterized by the fibrotic transformation in the oral mucosa, which causes the mouth to gradually shrink and makes breathing, speaking, and swallowing difficult. Numerous factors contribute to the development of OSF, although the root cause is still being explored.[1] The precise etiology of the illness is unknown, it is thought that a number of important factors, such as immunological response, environmental exposures, genetic vulnerability, and cellular alterations, contribute to its progression. In order to better understand the molecular, cellular, and clinical aspects of oral submucous fibrosis, the following review will examine the different pathways that contribute to its etiology. Oral submucous fibrosis is a disease with a multidimensional pathophysiology that includes genetic, environmental, immunological, and cellular components.[2] Excessive collagen deposition and fibrosis in the oral mucosa is brought about by the combination of persistent irritation, particularly from tobacco and areca nut, and the activation of various cellular and molecular pathways.[3] Considering OSF is a precancerous condition with a high chance of transforming into oral cancer, patient management is contingent upon detection and intervention. The development of tailored treatment approaches designed to stop or reverse the fibrotic process to improve the quality of life for those impacted by OSF demands an understanding of the disease's pathophysiology.[4,5]

INITIAL EVENTS OF THE DISEASE

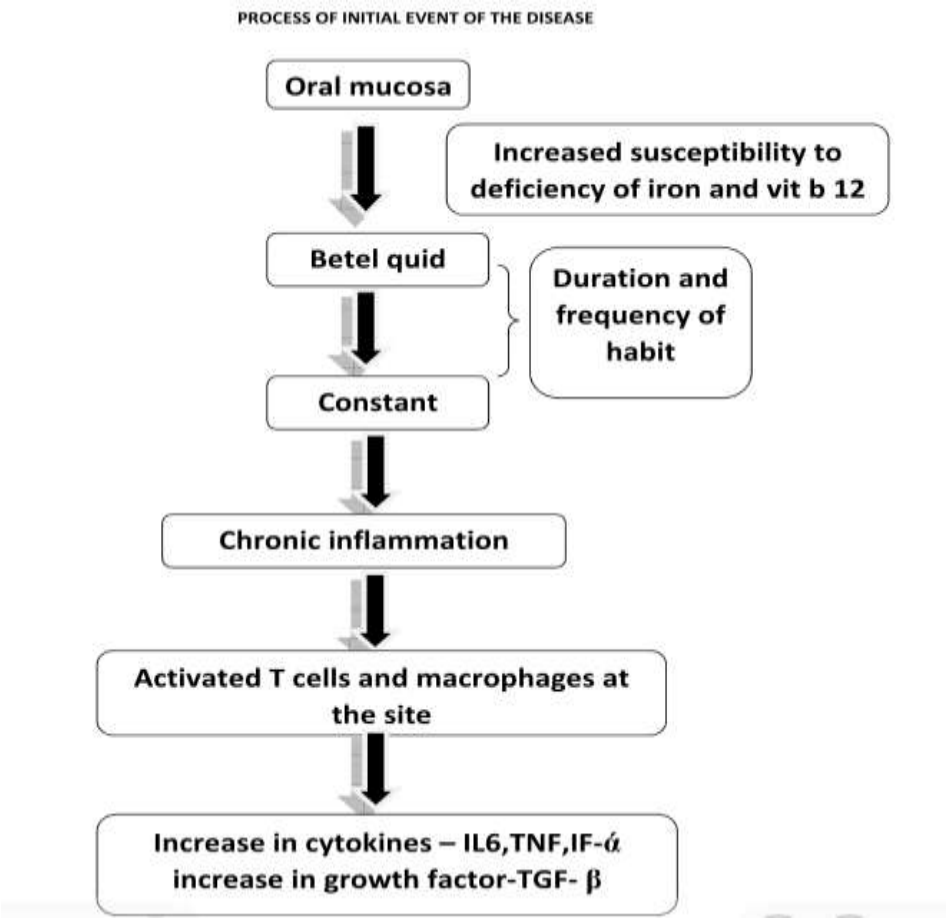
When betel quid is chewed, the combination and the oral mucosa come into constant touch. The flavonoids and alkaloids in Beetle quid are digested and absorbed. The components and their metabolites cause continuous irritation of oral tissues (Fig. 1). The oral mucosa becomes mechanically irritated by the abrasive fibres of areca nuts in addition to the chemical irritation brought on by beetle quid components and their metabolites. Furthermore, because of the microdamage caused by the friction of areca nut coarse fibres, beetle quid alkaloids and flavonoids seep into the subepithelial connective tissue which results in juxtaepithelial inflammatory cell infiltration. A protective inflammatory response can be triggered by any external event that causes tissue damage. Long-term conduct causes chronic inflammation to develop at the site (Fig. 1). Which is followed by excess atrophy and initial discomfort.[6]

Beetle quid is a substance or combination of substances that are chewed or put into the mouth while staying in connection with the mucosa. In its raw, processed, or manufactured forms, it typically contains one or both of the two main ingredients, tobacco and/or areca nut. Salted lime, catechu, areca nut (betel nut), and additional seasonings wrapped in betel leaves make up Beetle quid in the majority of places. The endosperm found in Areca catechu fruit is called an areca nut. Chewing betel has numerous benefits, including exhilaration, increased salivation, satiation of hunger, relief of tooth discomfort, and more. The primary areca nut alkaloids are guacine, guyacoline, arecoline, arecaidine, and arecolidine. [7] The primary flavonoid constituents of areca nuts are tannins and catechins. [7] The most common alkaloid is arecoline. N-nitrosamines are produced when these alkaloids undergo nitrosation, and they have the potential to be cytotoxic to cells. Arecoline has been shown to promote the synthesis of collagen[8].

Typically, the Beetle quid is chewed or placed in the buccal vestibule five to six times a day for 15 to 60 minutes, though individual chewing patterns vary, the mixture stays in constant touch with the mucosa of the mouth, the flavonoids and alkaloids included in Beetle quid are metabolized

and absorbed. Oral tissues are continuously irritated by these substances and their metabolites, apart from the chemical discomfort caused by Beetle quid components and metabolites, the mouth mucosa is mechanically irritated by the rough fibers of areca nuts additionally, the microtrauma brought on by the coarse areca nut fibers friction encourages Juxta epithelial inflammatory cells invade the subepithelial connective tissue by the entry of Beetle quid alkaloids and flavonoids. A defensive inflammatory response might be triggered by any external stimulus that damages tissue. Repeated behavior causes chronic inflammation in the area over time (Fig. 1). More mucosal shrinkage and ulceration result from the first inflammation [10].

Activated T-cells, macrophages, and other immune cells are signs of inflammation (Fig. 1). The production of different chemical mediators of inflammation, particularly prostaglandins (PGs) is crucial.[11,12] It has been demonstrated that areca nut extract (ANE) causes oral keratinocytes to produce PGs.[14–15] Unusual and persistent tissue inflammation is necessary for the development of tissue fibrosis and cancer[11]. Thus, it might be said that the development of oral mucosal inflammation by Beetle quid components is one of the major processes in the etiology of OSF. Growth factors such as TGF-β and cytokines such as interleukin 6, tumor necrosis factor (TNF), interferon a, and others are produced at the site of inflammation (Fig. 1). Literature states, people who are anaemic due to iron or vitamin B12 deficiencies are particularly at risk.[16] This might be because more Beetle quid can be absorbed due to increased mucosal fragility. An essential modulator of Extra cellular membrane remodeling and assembly is TGF-β1. Through unclear intracellular routes, TGF-β primarily affects transcriptional levels of the genes involved in extra cellular membrane formation and degradation. The collagen production and degradation pathways, which are controlled by TGF-β and the flavonoids in arecanut, are the two categories into which this review splits the molecular events.

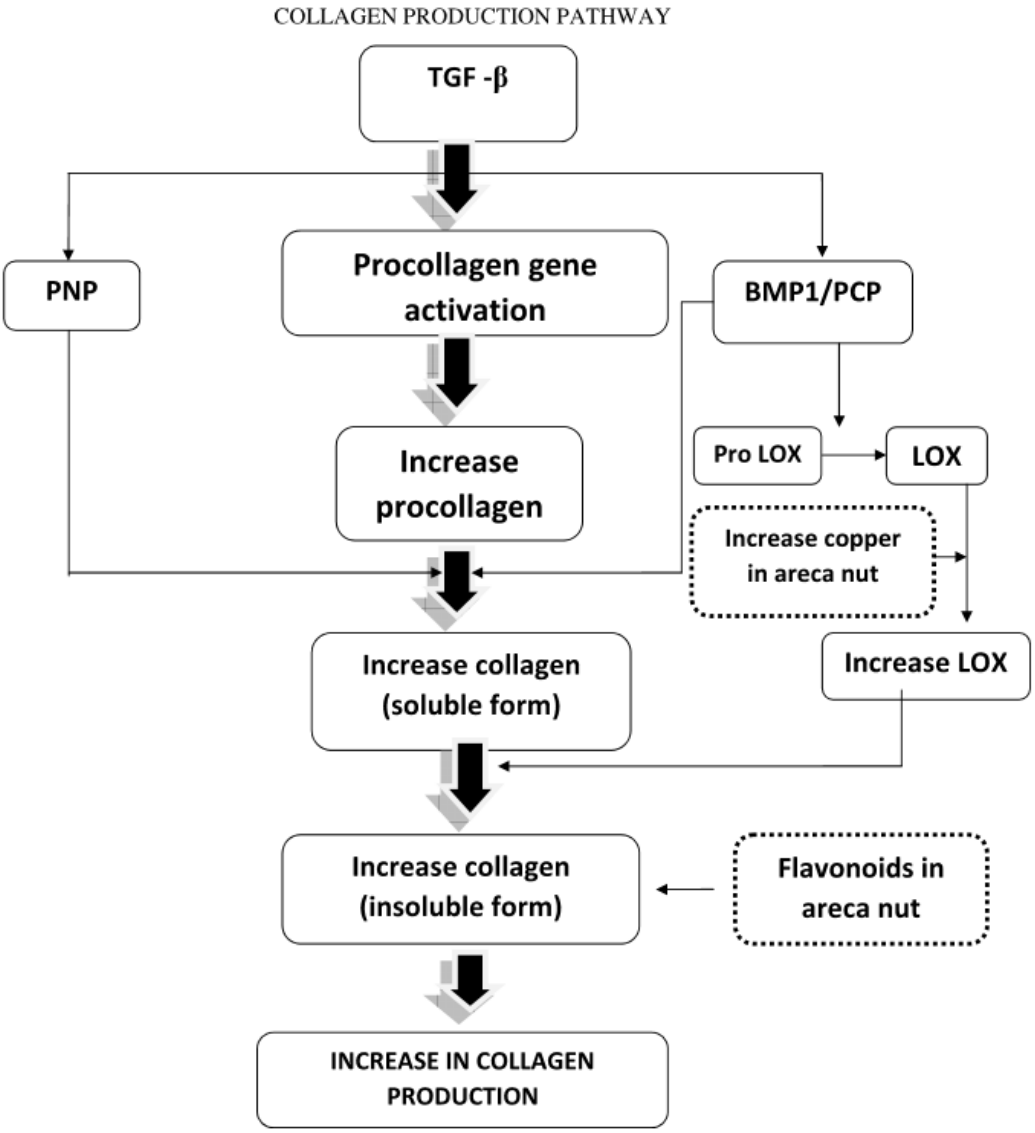


(Figure-1)

The three main processes that TGF-β influence to promote collagen production are (a) an increase in procollagen C-proteinase (PCP) or bone morphogenetic protein 1 (BMP1), (b) an increase in procollagen N proteinase (PNP), and (c) an increase in lysyl oxidase (LOX) activity (Figure 2).

(i) ACTIVATION OF PROCOLLAGEN GENES

The human body's most prevalent protein, collagen is essential for the structural integrity of connective tissue. Collagen has been found in about 27 different forms, which fall into seven broad classes. Types I, III, and VI of fibrillar collagen, the most common class, make up a sizable amount of connective tissue. The oral mucosa's anchoring fibrils are made up of collagen type VII. It is characterised by a unique triple helix that is strengthened by unusual cross-links. It takes time for fibrillar collagen to be processed.



(Figure-2)

COLLAGEN PRODUCTION PATHWAYAS REGULATED BY TGF- β

Procollagen genes undergo transcription and translation to produce procollagen monomeric chains, also known as procollagen precursors (Figure- 2). Three monomers combined to form a trimeric triple helix, which aids in disulphide bridge formation. Trimeric procollagen chains are then acted upon by N- and C-terminal proteases i.e., Procollagen-C-Proteinase (PCP) and Procollagen-N-Proteinase (PNP) to cleave the terminal domains. Collagen units spontaneously form fibrils after this cleavage. Cross-linking covalently stabilizes the freshly generated fibrils, producing a stable mature collagen structure[16]. TGF-β has been shown to target the genes COL1A2, COL3A1, COL6A1, COL6A3, and COL7A1 (Figure 2). These are genes which are initially induced by fibroblasts.. It has been shown that TGF-β transcriptionally activates the expression of collagen genes types I and VII. TGF-β causes procollagen genes to be transcriptionally activated, which increases their expression and raises the amount of collagen in OSF [16].

(ii) ELEVATION LEVELS OF PROCOLLAGEN PROTEINASES

Procollagen proteinases are necessary for the conversion of procollagen precursors into soluble collagen fibrils. The C-terminal and the N-terminal are known to be cleaved by two different types of proteinases: As seen in Figure 2, PNP and PCP.[17] The procollagen precursor's C-terminal is cleaved by the same protein PCP and BMP1.[18,19] both transcriptionally and translationally induced by TGF-β1 in numerous cell types, including fibrogenic cell cultures and osteosarcoma cells [20].

Procollagen N-proteinase (PNP)

PNP breaks down the procollagen precursor's N-propeptide [21] (Figure 2). Based on the particular procollagen fibers they target, PNPs are divided into two types: PNP I and PNP III [22,23]. PNP levels are higher in cells treated with TGF-β. Procollagen genes are expressed more when TGF-β is present, and processing into fibrils is enhanced by elevated N- and C-procollagen proteinase levels and activity [23].

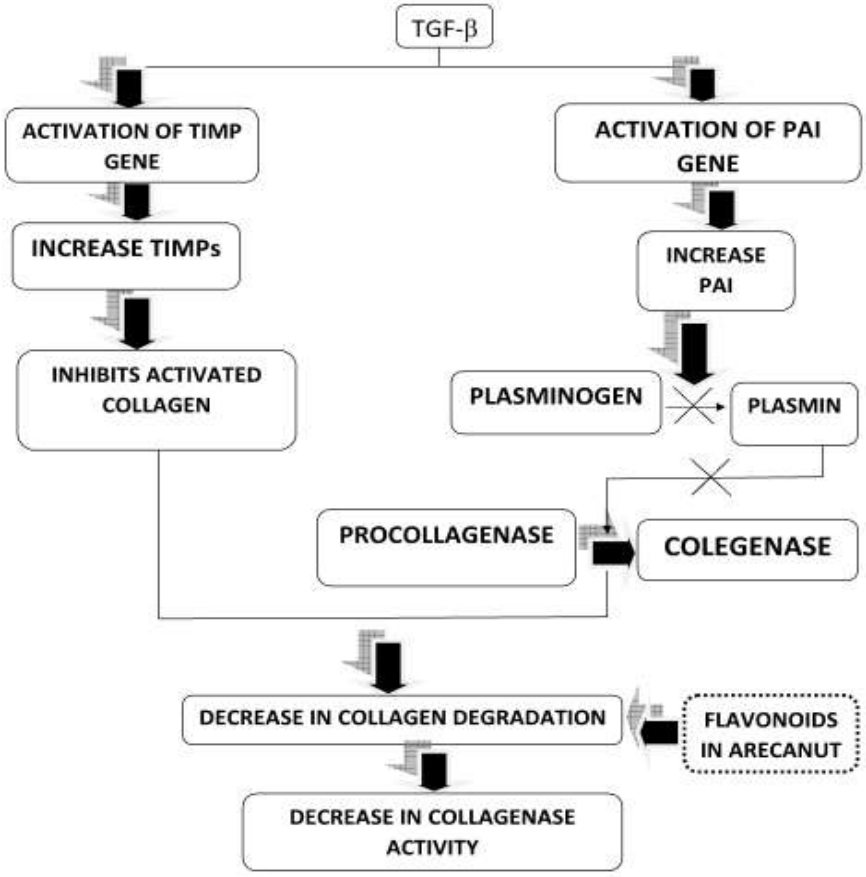
(iii) UPREGULATION OF LOX ACTIVITY

The final processing of collagen fibers depends on the LOX enzyme, which helps transform them into a mature fibrillar form that is stable, covalently cross-linked, and resistant to proteolysis copper is necessary for the LOX to function, an apoenzyme that lacks copper is catalytically inactive. [24,25] Prolysyl oxidase is the precursor of LOX, and BMP1 mediates its transformation into active LOX in the extracellular environment (Figure-2)[26]. Copper is incorporated into LOX during the production of LOX. Apart from copper, LOX also contains lysine tyrosylquinone (LTQ). [27,28] The response mechanism of LOX, particularly the creation of cross-links within collagen fibers, depends on the.[29] Copper is proposed to have a structural role in stabilizing lysine tyrosylquinone.[30] Copper is essential for reoxidising the reduced enzyme during the cross-linking step, which makes it easier to finish catalytic cycle [28]. Because areca nuts have a high copper concentration, chewing them for five to thirty minutes raises the amount of soluble copper in oral secretions. By encouraging fibrogenesis through the upregulation of LOX activity, the increased concentration of soluble copper may have a substantial impact on OSF. [31,32]

Furthermore, the flavonoids in areca nuts have been linked to improved collagen fiber cross-linking. Research has demonstrated that catechin raises LOX activity in vitro. [33–34] They might be converted to quinones by oxidation, which would make them resemble LTQ, a crucial LOX activity co-factor. This might be among the causes of the rise in LOX activity.[35] Furthermore, Insilco molecular modelling studies have demonstrated that flavonoids directly interact with collagen to promote collagen fiber cross-linking.[36]

There are several variables that affect the regulation of LOX expression, but TGF-β has been found to play a major role (Figure 2). In several cell lines, TGF-β dramatically increases LOX expression at the mRNA and protein levels.[37,38] The exact process driving this event remains not entirely clear. The biosynthesis of LOX, specifically the transformation of prolysyl oxidase into active LOX, is mediated by TGF-β may indirectly cause this by elevating BMP1. [26]

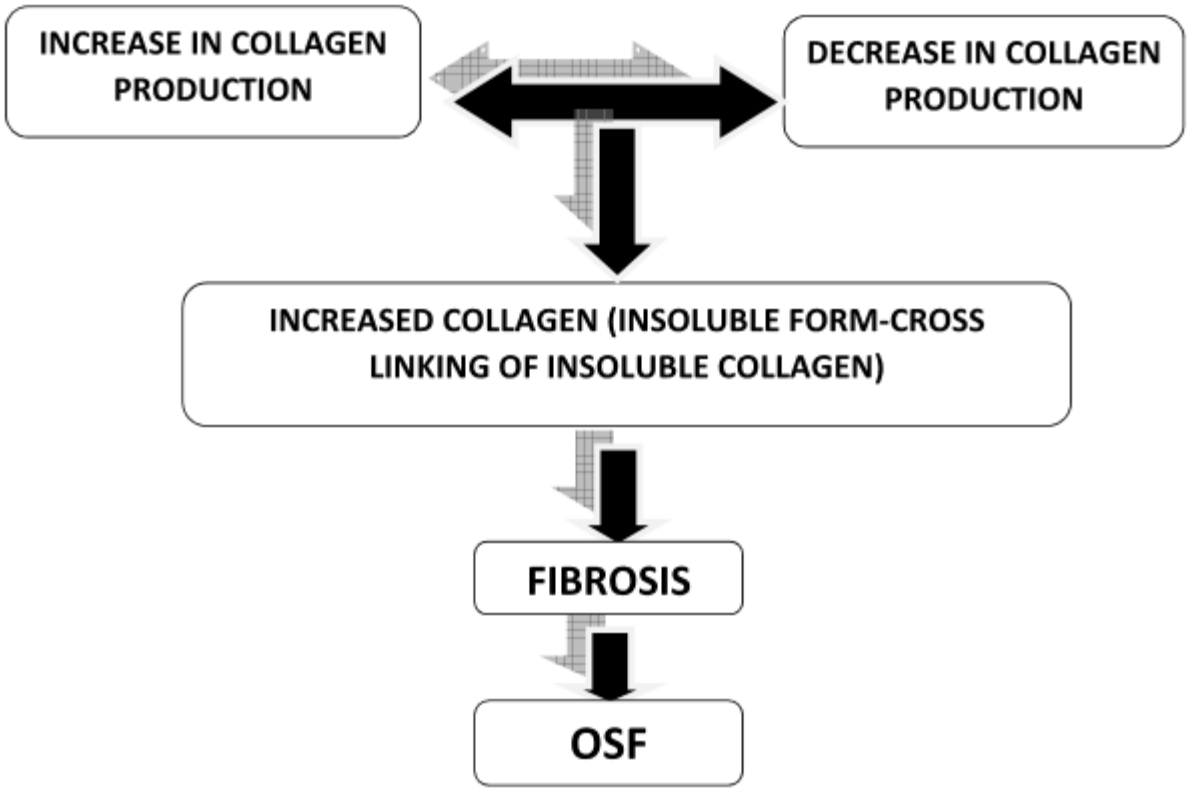
The production of insoluble collagen through cross-linking depends on LOX activity. In addition to making collagen fibers resistant to proteolysis, cross-linking improves the mechanical qualities and tensile strength of fibers. Collagen fiber cross-linking is improved by elevated LOX levels and activity, which are linked to higher BMP and copper concentrations, as well as further stimulation from LTQ-like flavonoids present in BQ. As seen in OSF, this change exacerbates the fibrotic disease[16].



(Figure-3)

COLLAGEN DEGRADATION PATHWAY

This review characterizes OSF as a disorder of collagen metabolism. Enhanced collagen synthesis and reduced collagen breakdown contribute to elevated collagen accumulation in oral tissue, resulting in fibrosis. This condition is made worse by the auto-regulatory mechanism of TGF-β, which is the primary factor responsible for both decreased degradation pathways and increased collagen production.[38]



OVERALL EFFECT OF ACTIVATED TGF-β PATHWAY
(Figure 4)

CONCLUSION

Oral submucous fibrosis is documented as a multifactorial disease and known to be associated with complex pathogenesis which involves genetic, environmental, immune, and cellular factors. The interaction between chronic irritation, particularly from areca nuts and tobacco, and the activation of various cellular and molecular pathways leads to excessive collagen deposition and fibrosis in the oral mucosa. OSF is a precancerous condition that has a significant chance of developing into oral cancer, highlighting the importance of early diagnosis and intervention in patient management. Comprehending the pathogenesis of OSF is crucial for formulating targeted therapeutic strategies that aim to halt or reverse the fibrotic process and enhance the quality of life for those affected.

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