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REVIEW ARTICLE **OPEN ACCESS**

Association between Serum Creatinine Kinase and Oral Submucousal Fibrosis

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ABSTRACT
The Oral Submucous Fibrosis occurs mostly in India and in South East Asia but the cases have been reported worldwide like Kenya, China, UK, Saudi Arabia and other parts of the world where Asian are migrating. According to Scully C., Oral carcinoma develops in as many as 10 % of patients of OSF 6. Another study which was done in India had shown that the transformation rate is as high as 7.6% . This review aims to find other confounding factors and variables, if any, associated with Oral Submucous Fibrosis.
Keywords: Submucosal Fibrosis, Creatinine Kinase ,Diabetes ,Collagen related genes (COL1A1)

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INTRODUCTION

Oral submucous fibrosis (OSF) is a chronic, insidious, disabling disease involving oral mucosa, the oropharynx, and rarely, the larynx [1].OSF is a premalignant disease. The primary etiological factor is areca (betel) nut chewing, other factors also include vitamin deficiency or hypersensitivity to various products. The condition is due to impaired degradation of normal collagen by fibroblasts rather than excess production[2]. The fibrous bands form bilaterally, initially in the faucets and then in the buccal mucosa and labial areas, as the disease progress the band on either side meet on the floor and roof of the mouth, forming a fibrous ring [3]. Bands are common at the back of the mouth in mild cases of oral submucous fibrosis and, as the disease increases in severity, are more likely to be found anteriorly as well[3,4]The fibrosis also leads to difficulty in mastication, speech, swallowing and pain in the throat and ears. It may lead to relative loss of auditory acuity because of stenosis of the opening of the Eustachian tube. In advanced cases, there may be severe trismus, and the totally inelastic mucosa is forced against the teeth, leading to chronic ulceration and subsequent infection [5].

PREVALENCE AND ETIOLOGY OF ORAL SUBMUCOUS FIBROSIS

Exact etiology of OSF is unknown; there are studies which had been done for the Betel quid consumption and their effect on Oral Mucosa. Oral submucous fibrosis is a caused by chewing of betel quid (Areca catechu). It is chewed regularly in South and South East Asia including Indonesia, Malaysia, Philippines, China, Taiwan, Papua New Guinea, Cambodia, Vietnam, Laos, India and Pakistan [5] Another study done in Pakistan for the relative risk of chewing Areca nut, the male/female risks were found to be similar. Immigrants from India to Pakistan (Mohajir) had a similar risk status to local Punjabis[6,7] Betel quid independently contributes to the risk of oropharyngeal cancer, oral leukoplakia [8], oral submucous fibrosis (OSF) [9].

PATHOGENESIS

The role of the constituents of areca nut in the pathogenesis of OSF had been studied in detail for the last two decades and several mechanisms are taught to be involved in the pathogenesis of OSF. Study on Areca nut, cause DNA damage , cell proliferation and cytotoxicity, in cultured fibroblast of oral mucosa [10].In vitro studies on human fibroblast using areca extracts or chemically purified arecoline support the

theory of fibroblast proliferation and increased collagen formation that is also demonstrable histologically in human OSF tissue[8,9].Collagen related genes COL1A1, COL1A2, COLase, TGF-β1, LYOXase and CST3 are also affected by the high betel quid exposure[11,12].

MALIGNANT TRANSFORMATION:

Histologically OSF is a premalignant condition characterized by juxta-epithelial fibrosis with atrophy or hyperplasia of the overlying epithelium which also shows areas of epithelial dysplasia. Paymaster in 1956 first discussed the precancerous nature of OSF, noted the onset of a slowly growing Squamous cell carcinoma in one-third of such patients [13,14]

DIAGNOSIS

Diagnosis is based on a positive history of chewing betel nut and other related compounds, excluding other factors which are responsible for causing limited mouth opening other than clinical features of OSF[15.16] Symptoms include burning sensation in the mouth when consuming spicy food, difficulty in mouth opening, appearance of blisters especially in palate [17] Ulceration and recurrent generalized inflammation of the oral mucosa, excessive salivation and dryness of the mouth [18]. Slow progression of disease makes any sort of diagnostic criteria difficult, at earlier stages of disease[19] Impairment of tongue movement in OSF affected patients in advance disease, atrophy of tongue papillae had also been observed in some cases [20].

HISTOLOGY OF NORMAL ORAL MUCOSAL EPITHELIUM:

The moist lining of Oral cavity which communicates with exterior is called oral mucosa[21] The oral mucosa consists of Stratified Squamous epithelium, primary barrier between the oral environment and deeper tissues, and an underlying connective tissue. Stratified Squamous epithelium arrange in number of layers, its structural integrity is maintained by a process of continuous cell renewal by mitotic division in the basal layer, migrate to the surface to replace those cells that are shedding with time. Mitotic activity can be affected by factors such as the time of the day, stress, and inflammation. Slight sub-epithelial inflammatory cell infiltrates stimulates mitosis, whereas severe inflammation causes a marked reduction in proliferative activity [22].

CREATINE KINASE

Creatine Kinase (CK) is an enzyme which is required for the phosphorylation of creatine to form creatine phosphate when muscle is in relax state. The serum level of CK is a marker of the functional status of muscle tissue and varies widely in both pathological and physiological conditions. Normal total CK values are 10 -50 IU/L at 30° C [20].

There are three isoenzymes of CK and their normal values.

- Skeletal muscles (CK-MM) 97% - 100%
- Cardiac muscles (CK-MB) 0% -3%
- Brain (CK-BB) 0 % [20]

All three isoenzymes of CK are present throughout the GI tract and that the majority of CK found is in the muscularis layer (MSL). CK-MM, presumably from striated muscles, was most prevalent in the esophagus [23]. Any damage to the musculature leads to high serum levels of CK. Accurate history and a correct diagnostic approach help the physician to formulate the correct diagnosis.

Total CK levels depend on age, gender, race, muscle mass, physical activity and climatic condition[24]. Normally, only CK-MM is present in the serum, but prolonged and strenuous exercise increases the serum activity of all three CK-isoenzymes in the absence of myocardial damage[25].

CREATINE KINASE RELATIONSHIP WITH ORAL SUBMUCOSAL FIBROSIS

OSF is a chronic premalignant disease, in OSF, chemical injury to muscles, due to the release of alkaloids, leading to fibrosis of the oral musculature. CK shows elevation when there is a chemical injury to the muscle as a result of damage to the sarcomere of the muscle fiber. There is a rise in CK before the sign and symptoms related to that of skeletal muscles.. Human buccal mucosa was consistently more permeable *in vitro* to arecoline compounds [26].Arecoline shows cytotoxic effect on human buccal fibroblasts cells *in vitro* studies[27]. In OSF there is damage to the muscle fiber. Both superficial and deeper fibers are affected by fibrosis as the disease advances[15] Therefore we think that in OSF cases CK would be altered, due to the trauma induced from the etiological agents.

CONCLUSION

There is association between serum Creatinine phosphokinase and Oral Submucous Fibrosis. There is need to screen high risk individual for the Serum creatinine Kinase level to prevent the advance sub mucosal fibrosis.

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