Potentially Significant Biomarkers in Oral Submucous Fibrosis

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INTRODUCTION

Oral submucous fibrosis is a precancerous disease with insidious onset and it is persistent, will result in activation oncogenes and loss of tumor suppressor genes that will promote abnormal cell growth and risk of oral cancer [1]. It is described as "Atrophic Koilocytic of mucosa oris" by Schwartz [2] in 1952 in Indian women in Kerala which can be described as insidious, chronic disease by Pindborg [3] in 1946 in any part of oral cavity and pharynx. 2. Oral submucous fibrosis is non-cancerous or superficial disease all over the world and has the highest potential of malignancy among other premalignant lesions [4]. The malignant rate of transformation over 17-year period was 7.6%. Trace elements (part of metalloenzymes) are recognised as versatile biomarkers which may be helpful in early detection, prognosis and can reduce the incidence of cancer [5]. Copper, Zinc, Nicotine, Cadmium, antioxidants (Superoxide Dimutase, Vitamin A, Vitamin C, Vitamin E), immunoglobulins and alternation in oncosupressor genes and other genes have been emphasized as biochemical parameters that play an important role in its pathogenesis. These parameters can also serve as important biomarkers in early detection of a premalignant condition and cancer progression.

Key Words: Oral submucous fibrosis, trace elements, biomarkers, antioxidants, oncosupressor genes

MATERIALS AND METHOD

This review included all articles that were used for the advancement of information about potential biomarkers in oral submucous fibrosis. Appropriate articles were determined according to a consideration of abstracts. Search of academic and published literature was carried out utilizing the electronic databases of Pub Med, Google scholar, Elsevier from 2000 to 2014 for English-language articles. The research terms applied were: "Biochemical markers and Oral Submucous Fibrosis", "Biomarkers of OSMF and OSMF", "The subjects, titles and abstracts of articles were appraised. Entire and complete text matter and reviews of the studies and researches were analysed when the abstracts pointed to the inclusion framework. Evaluation of selected data include a serious and detailed review of abstracts or full text papers.

Trace elements

Copper

Copper is the nutrient essential to carry out enzymatic functions important for human metabolism, including cysteine-c, oxidase, superoxide dimutase, metal thionein and lyl oxidase. In vitro, raised copper concentrations show increase proliferation of fibroblasts. High copper and ceruloplasmin levels were observed in patients with pre-malignant and malignant oral lesions. Areca nut has a high copper content (300 mmol/g), the substantial amount of which is related to saliva after 15-30 minutes of chewing areca nut [6]. Some studies show that high serum copper is responsible for the severity of OSMF [7]. Margalith et al investigated that damage by copper ions is due to superoxide radicals. These complexes react with hydrogen peroxide to form hydroxyl radicals that cause destruction of RNA, DNA and protein ultimately resulting in the malignancy [8]. The reason behind increased serum copper might be the reaction of copper containing the ceruloplasmin due to inflammatory response by liver or reduced degradation of serum ceruloplasmin. Cysteine-copper complexes have a role in pathogenesis of OSMF showing intense staining in arecanut chewers. Thus, it can prove an efficient marker of early diagnosis of malignant transformation [9].

Iron

Epidemiologic studies have established the role of diet rich in vegetables and fruits in oral carcinogenesis, with important contribution of vitamins and iron in maintenance of oral mucosa [10]. Iron plays an important role in development, maintenance and defense abilities of oral mucosa. It effects the ability of iron containing enzymes which require heme, biological oxidations, transport and is necessary for DNA, RNA, collagen and antibody synthesis [11]. Anemia can be treated by iron increase by oral intake, either by diet diversification, supplementation, or fortification of foods. The best long term approach in reduction of the incidence of iron deficiency is food fortification [12].

Oral submucous fibrosis is also considered as an "Asian version of Scleroderma dysphagia". Chronic iron deficiency leads to mucosal exposure to inffants such as arecanut. Phenyl hybrid hydroxylase requires molecular oxygen, ferrous iron, alpha-ketoglutarate and acetic acid to form collagen type I coupled with loss of more soluble collagen type III and type IV. In eastern countries, Oral submucous fibrosis (OSMF) may be the manifestation of chronic iron deficiency which is a counteract of Plummer-Vinson syndrome. The reasons of iron deficiency in OSMF is not clearly understood. Dietary iron may be due to its utilization in collagen formation by the process of hydrolysis of protein and lyne, altered epithelial cell turnover or decrease in iron intake, or decrease in iron absorption or diet inadequacy [13].

Zinc

Zinc (Zn) is an important part of biomembranes that manages membrane stability and lipid peroxidation related injury. It has a role in RNA and DNA, polymerase, inhibitory effect on phosphodiesterase, activation of membrane-bound adenycyclase thus suggesting a role of zinc in carcinogenesis. Some deficiency also contributes to cancer initiation by activation of NF-KB expression and the consequent induction of tumorigenic signaling [14].

Selenium

Selenium (antioxidant nutrient) has been considered as an integral part of the glutathione peroxidase enzyme, type I (iodothyronine deiodinase, metalloprotein, fatty acid binding protein and selenoprotein P) [15]. Low serum, plasma or blood levels of selenium have been found to be associated with the incidence of malignant lesions of the oral cavity [16,17], breast [18], ovary [19,20], esophagus [21], colon [22] and prostate [23]. Zinc and selenium have different functions important for human metabolism, including iron utilization in collagen for type III and type IV [24]. It is responsible for the production of type II collagen for tissue healing. Selenium has a role in RNA and DNA polymerase, effect by reducing zinc anticancer activity [25]. Some studies show selenium intake is of great benefit against cancer [26].

Cadmium

Rajendran et al [27] noticed elevated cadmium (Cd) levels in OSMF where as cadmium values were decreased in Oral Cancer and oral leukoplakia. Cadmium accumulates in the body hence cadmium burden increases with age. Increase intestinal absorption of Cd (a component of gutka) can be linked to low iron status in OSMF patients. The Cd can replace zinc (anti cariogenic agent) and will show its cariogenic effect by reducing zinc anticancer activity [28]. Cadmium may be one of the cause for malignant transformation of OSMF and its estimation may be a helpful tool in differential diagnosis of premalignant and malignant lesions of the oral mucosa.

Antioxidants

Reactive oxygen species (ROS) generation initiates lipid peroxidation (LPO) which highly promotes the carcinogenesis process. Antioxidants especially enzymatic antioxidants like Superoxide Dimutase (SOD), beta carotene and Vitamin A, Vitamin E, Vitamin C also play an important role in this process [29]. Stathen et al in his 12-year research on vitamins, plasma antioxidants and subclinical cancer mortality proved that decrease levels of antioxidants such as beta carotene, Vitamin C and Vitamin E play an important role in this process [30].
Superoxide Dismutase
Betel quid generates free radicals in the oral cavity. It is initiated by lipid peroxidation while enzymatic antioxidant superoxide dismutase detaches the effect of these harmful radicals (hydrogen peroxide and hydroxyl). These radicals transfer their unpaired electron to oxygen to form superoxide in order to prevent oxidative stress. Beta carotene and Vitamin A
Beta carotene (red-orange coloured pigment) is abundantly present in plants and animals. It is the inactive precursor of Vitamin A. Beta carotene ingestion quickly increases helper T lymphocytes. It plays an important role in OSMF and its level decreases with disease progression. An irreversibly oxidised form of Vitamin A is retinoic acid which is the principal hormone-like growth factor for maintenance of epithelial and other cells (7). It has immune-regulatory properties and an excellent radical trap for hydroxyl and peroxyl radicals, therefore it should be maintained in adequate levels in the blood.

Vitamin C (Ascorbic acid)
Vitamin C is an antioxidant scavenging free radical, reduces vitamin E degradation, inhibits nitrosamine formation, enhances detoxification via cytochrome P450 and iron absorption by reducing dietary iron from ferric form to the ferrous form. Vitamin C is utilized in conversion of proline into hydroxyproline. This hydroxylation reaction requires ferrous ion and Vitamin C. Lysyl oxidase upregulates the collagen cross linkages in the presence of Vitamin C that results in the advancement of the condition from stage I to stage II. Rajendran et al proved that deficiency of vitamins and iron will result in abnormal repair of the lamina propria. This will result in defective healing and scar formation, which ultimately led to OSMF. Singh et al concluded that the therapeutic supplementation of Vitamin C reduces the odema between the collagen bundles and regenerates new collagen bundles with good approximation in OSMF patients.

Vitamin E
Vitamin E is the fat soluble antioxidant that include both proline and hydroxyproline. This hydroxylation reaction requires ferrous ion and Vitamin C. Lysyl oxidase upregulates the collagen cross linkages in the presence of Vitamin C that results in the advancement of the condition from stage I to stage II. Rajendran et al proved that deficiency of vitamins and iron will result in abnormal repair of the lamina propria. This will result in defective healing and scar formation, which ultimately led to OSMF. Singh et al concluded that the therapeutic supplementation of Vitamin C reduces the odema between the collagen bundles and regenerates new collagen bundles with good approximation in OSMF patients.

Immunoglobulins
The role of active immune response in OSMF is to accelerate body protection and detection of the foreign antigen. This process will cause abnormal lymphocyte function and hyperactivity of B cells. High levels of IgG were observed in stage I OSMF patients. Studies show that OSMF or oral cancer. Oral Oncol 2013; 49: 887-92.

The cytochrome P450 (CYP) gene family function in oxidative metabolism of active endogenous and xenobiotic substrates. Cytochrome P450 has been identified as a genetic biomarker for susceptibility to OSMF and authors have further suggested that individuals with high genetic risk for OSMF could be investigated according to the genetic polymorphisms in some exclusive regions of the Cytochrome P450 3A genes. Genetic link CYP2BC1, CYP2F1, CYP3AS1, microsomal glutathione S-transferase 2 (UGT2B15), UDP glucuronosyl transferase 2B (UGT2B1), ADH1C related to the pathway of CYP metabolism were found to be down regulated in all stages of OSMF. It is suggested that these polymorphisms can be the cause of high risk of OSMF among men if they use arecanut or smoke tobacco in abundance.

CONCLUSION
Oral submucous fibrosis has a high incidence and carries a significant morbidity rate due to its progression to oral cancer. Occlusion of areca nut and gutkha products should be the first step among such patients. Intervention studies and public health awareness programmes linked with hazards of carcinogenic products (areca nut and gutkha) has become the common trend in the Asian society. OSMF conditions and habits may prove the best way to control the disease process at community level. The evaluation of trace elements put the clinician in a better position to determine the stage of precancerous condition and also highlights the importance of iron supplementation and healthy diet as a part of overall treatment of this disease.

REFERENCES
Table 1: Classification of Potential Biomarkers in OSMF

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<tr>
<th>Potential Biomarkers</th>
<th>Role in Oral Submucous Fibrosis (OSMF)</th>
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<tr>
<td>1) Proteins</td>
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<td>2) Antioxidants</td>
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<td>3) Immunomarkers</td>
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<td>4) Oxidative stress</td>
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References: