



Assessment of Serum Biomarkers in Oral Submucous Fibrosis for Prescription of Planned Diet: A Study Protocol

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Oral submucous fibrosis is common and aptly a chronic condition affecting oropharyngeal structure. Characteristically it shows burning mouth sensation, mucosal stiffness with reduced mouth opening and difficulty to eat. There are many treatment options but no single treatment has proven effective. Impairment of genomic structure by ROS may initiate and promote carcinogenesis. Physiologic antioxidants work together with exogenous antioxidants to curtail effects of ROS. Vitamins E and C are especially important among the external antioxidants. OSMF is premalignant condition and is consistently associated with betel nut and tobacco like carcinogens, so may have connotation with ROS.

Objective: To determine levels of iron, zinc, copper, vitamin A, C, E within serum of oral submucous fibrosis patients to conceptualize diet plan for different grades of OSMF according to need of the patient.

Method: The present study will be conducted in 50 cases of OSMF. Five milliliters of venous blood will be obtained of each participant from the antecubital vein using 24-gauge needle. The blood

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samples will be centrifuged and stored. Analysis of serum for iron, copper, zinc, and vitamins A, C and E will be done subsequently with ELISA diagnostic kits for these biomarkers respectively.

Results: Serum analysis will show low levels of iron, copper, zinc, vitamin A, C and E which may act as contributing factor in the etiology of OSMF. Depending on the deficient element, diet plan will be prepared according to the need of the patient.

Conclusion: Incidence of mouth cancer is expected to rise in near future because of increase in prevalence of oral submucous fibrosis. Altered nutritional status may be an important factor in causation of OSMF. Assessing biochemical changes will help in determining the nutritional status of patient. This will help in prescribing nutritional diet for patients suffering from OSMF.

Keywords: Serum biomarkers; oral submucous fibrosis; antioxidant vitamins; iron; copper; zinc.

1. INTRODUCTION

Oral submucous fibrosis (OSMF) is common and aptly a chronic condition affecting oropharyngeal structure. Characteristically it shows burning mouth sensation, mucosal stiffness with reduced mouth opening and difficulty to eat [1]. "Potentially malignant disorder" [2]. is a correct description for oral submucous fibrosis as it carries high rate of getting converted into malignancy. None of the reports suggest spontaneous reversal to normal mucosa and there are many treatment options but no single treatment has proven effective [3]. This condition has largely affected parts of Asia and Indian subcontinent. The consistently associated habit with OSMF is areca nut (betel nut) chewing which is now accepted as etiology. High rate of occurrence in Asian people inclined to this habit has supported this issue [4].

Developing countries rather than developed has more occurrence of oropharyngeal cancer. Particularly men show high prevalence of oral cancer, which ranks eighth among common cancers worldwide. One of the three most common types of cancer is cancer of oral cavity in south-central Asia [5]. Incidence rate of oral cancer standardized according to age is 12.6 per 100 000 population, in India. Tobacco, unhealthy diet, physical inactivity and infections accounts for approximately 43% of cancer deaths worldwide. Approximately 90% of cancers in the oral cavity are due to tobacco use and excessive alcohol consumption; tobacco consumption along the alcohol or betel nut increases oral cancer risk [6].

Impairment of genomic structure by Reactive Oxygen Species (ROS) may initiate and promote carcinogenesis [7]. The ROS works by starting lipid peroxidation [8]. The ROS are constantly generated by the body and endogenous antioxidants may not be able to detoxify them

completely. The source of exogenous antioxidants is thus critical. Physiologic antioxidants work together with exogenous antioxidants to curtail effects of ROS. Although a large number of endogenous antioxidants functions, the primary contributors are superoxide dismutases, catalase, and the glutathione system. Vitamins E and C are especially important among the external antioxidants. Epidemiological studies have linked high intake of yellow and green vegetables like broccoli, cauliflower, mustard, cress, brussels sprouts with reduced risk of cancer [9].

Dietary risk factors have been suggested for causation of oral cancer. Oral cancer risk is reduced by intake of various vegetables and fruits as demonstrated by various studies. These associations may be separate from other risk factors and display a dose-response [10,11]. Oral cancer commonly occur in pre-existing oral premalignant lesions and conditions [12]. Equally, even after controlling tobacco habit factor conversion rate of oral premalignant lesions into cancer has been found to be very high [13]. Tobacco habit associated oral premalignant lesion proceed similarly to that of oral cancer [14].

The incidence of oral submucous fibrosis (OSMF) is increasing like a disaster, especially within the younger age group. Exact etiology of OSMF is still not known. Number of different etiologic factors have been suggested for OSMF amongst which betel nut chewing is the most consistent and important finding associated with patient's history [15]. Incidence of mouth cancer is expected to rise in near future because of increase in prevalence of oral submucous fibrosis [16]. OSMF is premalignant condition and is consistently associated with betel nut and tobacco like carcinogens, so may have connotation with ROS. Evaluation of biochemical changes in the serum of OSMF patients will be

helpful in the early diagnosis and correct treatment. Importantly such evaluation will identify markers of progression as the disease advances.

In cases of OSMF, there is progressive difficulty in opening of mouth due to deposition of abnormal fibrous bands in oral mucosa and burning sensation due to atrophy. Due to difficulty in opening mouth, there is always difficulty in mastication and swallowing. In addition, papillary atrophy of tongue leads to dysgeusia. Above factors leads to reduced intake of food which may be responsible for further worsening of OSMF. Assessing the biochemical changes will help in determining the nutritional status of patient caused due to altered intake of food. This will help in prescribing nutritional diet for patients suffering from OSMF.

Hence the present case-control study will be undertaken to assess levels of essential trace elements iron, zinc, copper and the antioxidant vitamins A, C, E within the serum of oral submucous fibrosis patients for prescription of planned diet.

1.1 Aim

Assessment of serum biomarkers in oral submucous fibrosis for prescription of planned diet.

1.2 Objectives

1. To determine levels of iron, zinc, copper, vitamin A, C, E within serum of oral submucous fibrosis patients.
2. To conceptualize diet plan for different grades of OSMF according to need of the patient.

2. METHODS

The study entitled "Assessment of serum biomarkers in oral submucous fibrosis for prescription of planned diet" will be conducted in Oral Medicine and Radiology department of Sharad Pawar Dental College and Hospital, Sawangi (Meghe), Wardha.

2.1 Inclusion Criteria

1. All new i.e., untreated patients presenting with OSMF, reporting to the department of oral medicine and radiology irrespective of their age and gender.

2.2 Exclusion Criteria

1. Patients of OSMF with suspicious malignant lesion, histologically proven malignant lesion or metastatic disease in the oral cavity.
2. Patients with previously treated OSMF.
3. Patients with long term review for dysplasia.
4. All patients with history of another prior malignant disease in the body.

The subject will be classified as a case if he has OSMF. OSMF will be diagnosed on the basis of clinical diagnostic criteria. The sample size for the study subjects (cases of OSMF) is 50 as calculated by statistician. Subsequently examined subjects without any lesion of oral mucosa will be selected as a control. Only after written informed consent, the eligible subjects will be involved in the study.

The OSMF patients will be divided into four grades according to functional staging [17].

- Grade I: 'Interincisal opening 35 mm or greater'
- Grade II: 'Interincisal opening from 25 to 34 mm'
- Grade III: 'Interincisal opening from 15 and 24 mm'
- Grade IV: 'Interincisal mouth opening less than 15 mm'

Five milliliters venous blood will be obtained of each participant from the antecubital vein using 24-gauge needle. The blood samples will be sent to Central Research House, DMIMS (DU), where it will be centrifuged and stored at -70°C . Further analysis of serum for iron, copper, zinc, and vitamins A, C and E will be done subsequently with ELISA diagnostic kits for these biomarkers respectively.

Due to chronicity of tobacco and betel nut chewing habit, the nutritional status of the patients gets altered. In such scenario it is also important to take into consideration the other confounding factors such as social and economic variables which may act as proxies for actually important risk factors.

2.3 Economic Classes

- High status: individuals having well-built concrete house; serving as government

officer or on higher post in private sector, having a successfully running business or shop and employing servants.

- Middle status: individuals having a small house without a concrete slab, in service of low-level government job or on lower post in private sector; owning a small shop without employing servants.
- Low status: unemployed individuals without their own house or own business and works as very small level worker at some shop or field.

2.4 Occupation

- Active – individuals working in farm or doing any type of labor work or having field duties.
- Sedentary – individuals having table work (does not have to do laborious work) at government or private sector or unemployed individuals who prefer to stay at home or individuals who works from home

2.5 Education

- Illiterate
- Primary school level education
- High school level education
- College graduate
- College post-graduate

We will define habit described as:

- Betel nut with tobacco including Kharra
- Betel nut with tobacco mixed with smoking
- Betel nut with tobacco mixed with alcohol
- Betel nut with tobacco mixed with smoking and alcohol

2.6 Statistical Analysis

All data will be analyzed using SPSS statistical software (version 16) (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). Descriptive statistics will be computed for all variables. Data are expressed as means \pm standard deviation. *t*-test will be utilized for comparative evaluation of different parameters between grades of OSMF and controls. Relationship between different parameters will be correlated using Karl Pearson correlation test. Also, one way ANOVA and multiple linear regression analysis will be carried out to find correlation between different variables and

OSMF. Statistical differences with a $P < 0.05$ will be considered to be significant.

3. EXPECTED RESULT

OSMF will result in low levels of iron, copper, zinc, vitamin A, C and E which may act as contributing factor in the etiology of OSMF. Depending on the deficient element, diet plan will be prepared according to the need of the patient.

4. DISCUSSION

The concentration of copper in saliva and tissues was found to be high in patients chewing areca nut products while copper concentrations in serum were within standard reference range [18]. Various studies have noted decreased levels of zinc and there was increase in copper/zinc ratio [19]. A study indicated that levels of vitamin E and beta-carotene decreased in OSMF patients [20]. When total serum protein and Ig levels were correlated, all patients with OSMF showed significant decrease in total serum protein [21]. This study suggests a nutritional factor for the OSMF.

It has been noted in OSMF that there is higher total iron binding capacity with significant reduction in concentration of serum iron. Use of iron in collagen synthesis might have caused this reduction. Additionally, decreased vascularity of oral tissues due to reduced iron levels eases entry of arecoline which further promotes collagen synthesis [22]. OSMF causes reduced iron levels due to altered diet is suggested by most studies but one study reported OSMF primarily due to iron deficiency anemia which was treated successfully by antioxidants and iron supplements [23]. It is found that with the increase in the stages of head and neck carcinomas ferritin levels are increased and iron levels are reduced in serum. So, the iron may be good biochemical marker during nutritional evaluation [24].

Numerous studies have noted higher levels of serum copper in OSMF and other premalignant and malignant disorders. These higher levels are due to betel nut chewing. This habit is prevalent in India. After areca nut chewing, released copper from betel nut directly comes in contact with oral mucosa and can be present for about 30 minutes in saliva and has higher chances of getting absorbed by epithelial layer [25]. After 15 minutes of chewing and deglutition of betel nut,

copper appears in blood [22]. Serum levels of copper increases with the severity of OSMF. It is the copper level in saliva than in blood which has to play crucial role in OSMF. Other studies states reduced levels of serum copper due to its role in excess cross linking of collagen from lysyl oxidase [26].

Another essential trace element zinc is a co-factor for endogenous antioxidant superoxide dismutase and numerous studies have found its lower level in serum in premalignant lesions in response to its increased usage in response to high levels of copper received after betel nut chewing or increased burden of oxidants produced after betel nut and tobacco usage [24]. Likewise zinc serum levels significantly decreases in cases with oral submucous fibrosis and oral carcinoma having tobacco and betel nut consumption history as compared to control subjects and the levels are gradually reduced with the duration of tobacco and betel nut chewing habit. Variation in levels of zinc exist between OSMF and oral carcinoma with more reduced levels in latter [22,27]. In iron deficiency anemia iron level decreases whereas zinc increases as for both zinc and iron transferrin is the transport medium. So, it is found that OSMF patients with iron deficiency anemia show increased zinc levels [22,27].

The activity of zinc is reversely proportional to copper interfering with its absorption. One of the endogenous antioxidants having anticarcinogenic effect is Superoxide dismutase which is made up of Cu-Zn protein complex. Zinc also plays indirect role in preventing cross linking of collagen fibers by decreasing the activity of lysyl oxidase enzyme containing copper. Zinc promotes collagen degradation through matrix metalloproteinase and collagenase. Absorption of copper is impaired particularly by excess zinc because both are absorbed through metallothioneins. Thus, the copper to zinc ratio can be utilized as trustable biochemical marker for assessment of progression towards premalignancy and malignancy [27].

The healthy status of the body is maintained through proper nutrition of metabolically active all the tissues and cells. Dealing with continuously produced stress of reactive oxygen species, supporting all the constantly occurring regenerative processes and boosting immunity

during infections are all conducted with the vital participation of micronutrients including antioxidant vitamins and trace elements [28,29]. There are so many oral manifestations of lack of proper nutrition or overnutrition and can manifest as diseases of oral hard and soft tissues [30,31]. So, a healthy nutritious diet containing all the vital trace elements and vitamins is essential for the oral health and general well-being.

Currently much emphasis has been put forth on essential and trace elements to evaluate whether such elements are involved in causation of oral precancer and cancer. Evaluation of biochemical changes in the serum of OSMF patients will be helpful in the early diagnosis and correct treatment. Importantly such evaluation will identify markers of progression as the disease advances. Thought of preconditioned mucosa has been argued from many years in search of causative factors in OSMF. Change in response to local factors has been noted in preconditioned mucosa because of nutritional deficiency [32,33].

Impairment of genomic structure by Reactive Oxygen Species (ROS) may initiate and promote carcinogenesis. Physiologic antioxidants work together with exogenous antioxidants to curtail effects of ROS. The primary endogenous contributors are superoxide dismutases, catalase, and the glutathione system. Vitamins E and C are especially important among the external antioxidants [9]. OSMF is premalignant condition and is consistently associated with betel nut and tobacco like carcinogens, so may have connotation with ROS. Related studies on OSMF were reported by Gondivkar et al. [34], Hande et al. [35] and Umate et al. [36].

Reduced opening of mouth, burning sensation, difficulty in mastication and swallowing leads to reduced intake of food which may be responsible for further worsening of OSMF. Assessing the biochemical changes will help in determining the nutritional status of patient caused due to altered intake of food. This will help in prescribing nutritional diet for patients suffering from OSMF. Hence the present case-control study will be undertaken to assess levels of essential trace elements iron, zinc, copper and the antioxidant vitamins A, C, E within the serum of oral submucous fibrosis patients for prescription of planned diet.

5. CONCLUSION

Incidence of mouth cancer is expected to rise in near future because of increase in prevalence of oral submucous fibrosis. Altered nutritional status may be an important factor in causation of OSMF. Assessing biochemical changes will help in determining the nutritional status of patient. This will help in prescribing nutritional diet for patients suffering from OSMF.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

Institutional Ethics Committee (IEC) has approved the study with reference number DMIMS (DU)/IEC/2018-19/7468.

CONSENT

As per international standard or university standard, patient's written consent will be collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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