Original Article

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Dentistry Section

Evaluation of Hearing Impairment and Levels of Trace Elements in Patients with Oral Submucous Fibrosis

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ABSTRACT

Introduction: Oral Submucous Fibrosis (OSMF) is a slowly progressive premalignant condition. Trace elements like Copper (Cu) and Zinc (Zn) were found to have diagnostic and prognostic values in malignancies. Disease activity at in an earlier stage by determining the exact stage of OSMF based on eustachian tube dysfunction and serum Cu, Zn, and Iron (Fe) levels.

Aim: To assess the Eustachian tube dysfunction and level of trace elements in OSMF patients.

Materials and Methods: This case-control study was carried out in VSPM Dental College and Research Centre Nagpur and Department of Ear, Nose and Throat (ENT) and Biochemistry of NKP Salve Medical College, Nagpur, Maharashtra, India, from March 2018 to February 2019. Two hundred patients were equally divided into individuals without OSMF and with OSMF. A Pure Tone Audiometry (PTA) was used to measure degree of hearing impairment while estimation of trace elements Cu, Zn and Fe was done by atomic absorption spectrophotometry. The unpaired t-test, Chi-square test and one-way Analysis of Variance (ANOVA) test were used for statistical analysis.

Results: All 200 individuals were matched with age and sex in both the groups. Normal hearing was found in 61% of the ears and Conductive Hearing Loss (CHL) in 39% of the ears with OSMF. A positive association of hearing loss in both the ears with stages of OSMF were seen which was statistically significant with p-value of 0.001. The level of Cu (103.44 mg/dL) was found increased in OSMF individuals while the levels of Zn (78.93 mg/dL) and Fe (84.05 mg/dL) was reduced.

Conclusion: Within the limitations of the study, there was association between the severity of OSMF, degree of hearing loss and levels of trace elements. One of the most serious side-effects of OSMF is hearing loss. Level of copper increased while level of zinc and iron were reduced in OSMF patients.

Keywords: Eustachian tube, Hearing loss, Nutritional deficiency, Premalignant lesion

INTRODUCTION

The OSMF is a slowly progressive premalignant condition commonly encountered in India and South Asian countries. It is characterised by fibrosis of oral mucosa leading to severe restriction of jaw and tongue movements [1]. The pathogenesis of OSMF has multifactorial origin including nutritional deficiencies, ingestion of chilies, habit of chewing areca nut, factors like pollution, genetic and immunologic processes. Various researchers have reported that OSMF affects the muscles of the soft palate like tensor veli palatine and levator veli palatine and subsequently may affect the Eustachian tube function and patency [2].

Trace elements like copper and zinc were found to have diagnostic and prognostic values in malignancies like lymphoma, carcinoma of lung and breast etc., [3]. Due to increased iron usage in collagen formation and subsequent reduced epithelial vascularity in OSMF, iron levels are decreased [4]. It produces erosion and fibrosis, as well as a burning sensation. Vesicle development precedes OSMF, which is linked to juxtaepithelial condensation. To distinguish healthy mucosa from OSMF-affected mucosa, clinical and histopathologic characteristics are often used. However, these technologies have the drawback of detecting disease at a later stage, necessitating intensive treatment, including non surgical and surgical therapy. As a result, treatment costs and patient morbidity rise [5]. It is preferable to predict future disease activity in earlier stage by determining the exact stage of "OSMF" based on Eustachian tube dysfunction and serum Cu, Zn, and Fe levels [6,7]. Literature is scarce on Eustachian tube function and trace elements leading to hearing impairment in OSMF. The early detection of OSMF and hearing loss, the provision of appropriate and limited therapy, and the reversal of the sickness state by proper prophylactic measures would all be aided by this. Therefore, the objective of this study was to assess hearing impairment in individuals with OSMF and compare it to Eustachian tube function and blood levels of Cu, Zn, and Fe.

MATERIALS AND METHODS

The present case-control study was carried out in Department of VSPM Dental College and Research Centre Nagpur and Department of ENT and Biochemistry of NKP Salve Medical College, Nagpur, Maharashtra, India. The study was initiated from March 2018 to February 2019. The study protocol was approved by Institutional Ethics Committee and which was abided by the Declaration of Helsinki of 1979 (revised 2000) and was registered in Clinical Trial Registry India (CTRI/2017/10/010161).

Inclusion criteria: Individual ranging between the age group of 13-35 years, healthy individual without OSMF (n=100), individual with OSMF (n=100), systemically healthy individual and patients who had consumed kharra for more than 3 years [8] were included in the study.

Exclusion criteria: Exclusion criteria were individuals with more than one type of lesion, undergoing treatment for OSMF, smokers and alcoholics, perforation of tympanic membrane, middle ear pathology and cholesteatoma, other condition causing restrictive mouth opening, having sensorineural hearing loss, having iron deficiency anaemia, history of drug intake containing iron, copper and zinc, pregnant women and patients on oral contraceptives.

Sample size calculation: The sample size was calculated based on the study by Shah M et al., [9].

Sample size calculation was done using the formula:

$$n=\frac{(Z_{\alpha/2}+Z_{\beta})^2\ (P^1(1-P_1)+(P_2(1-P_2))}{(P_1-P_2)}$$

Where, $Z_{\alpha/2}$ was the critical value for 5% significance level, which is 1.96, Zβ was the critical value at β. To attain 80% power of the

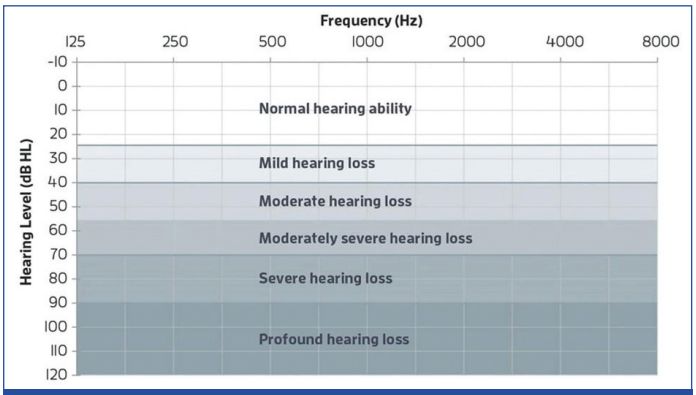
test, the value of β was 0.2 and thus the value Zβ was 0.84. Here, p1 and p2 the two-proportion, 'n' was the sample size per group. Using the estimates of reference study and above constants in the formulation, the estimated sample size per group was 99 (rounded to 100 per group). Thus, the total sample size was 200.

All the patients were categorised into two groups as control group without OSMF (100 patients) and case group with OSMF (100 patients).

Study Procedure

The OSMF patients were recruited according to the clinical staging of Khanna JN and Andrade NN in 1995 classification [10]. A Vernier calliper was used to measure the interincisal distance between the maxillary and mandibular central incisal edges and maximum mouth opening. A general physical examination was carried out to look for any gross debilitating condition.

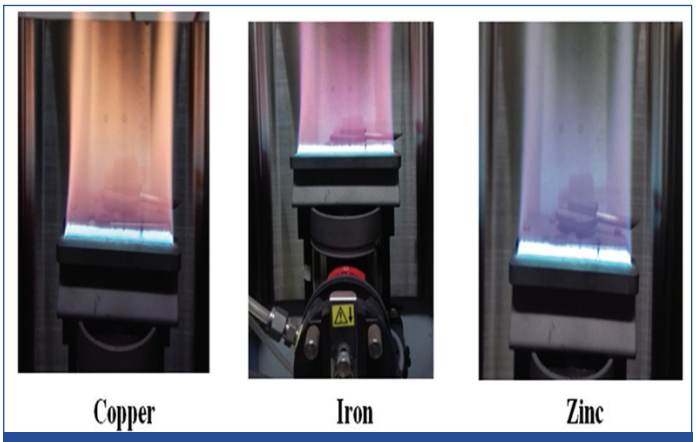
Audiological assessment was carried out in the Department of ENT. All the participants underwent otoscopy to rule out for any pathology associated with ear. Afterward the individuals with and without OSMF underwent procedure for PTA [3] to check the air Bone (AB) gap measurement for hearing impairement by ELKON Advanced Digital Audiometer in sound proof room. The PTA was performed to analyse Bone Conduction (BC) and Air Conduction (AC) threshold for tones from 250, 500, 1000, 2000 and 4000 Hz. The level of "hearing impairment" at a certain frequency was measured if the intensity was elevated over the normal level. "Hearing impairment" was quantitatively rated after reading the audiogram and relying on AC-BC gap values [Table/Fig-1] [11].



[Table/Fig-1]: Audiogram [11].
The X-axis shows frequency (pitch) from lowest to highest, and the Y-axis reflects intensity (loudness) for sound in decibels in the audiogram graph. Following the PTA, a hearing care professional would classify the severity or degree of hearing loss based on where the symbols sit on the graph

Biochemical analysis of trace elements [12-14] was done as follows:

For the serum preparation 5 mL venous blood was collected and stored at 37° C for one hour followed by centrifugation at 3000 rpm for six minutes. Separated serum was stored in a plain sterile glass bulb at 4°C and estimation of trace elements Cu, Zn and Fe was done by atomic absorption spectrophotometry [Table/Fig-2].



[Table/Fig-2]: Atomic absorption spectrophotometry.

STATISTICAL ANALYSIS

The data was recorded and analysed using Statistical Package for Social Sciences (SPSS) v 17. All values expressed in terms of Mean±Standard Deviation (SD). The p-value at 95% confidence interval was calibrated as the level of significance. The comparison of mean hearing loss was in decibels in OSMF and without OSMF group was done by unpaired t-test. The Chi-square test was used for comparison of hearing loss with stages of OSMF in left and right ear. The unpaired t-test was used to compare trace element in OSMF and without OSMF group. Unpaired t-test was used for comparison of hearing loss and trace elements with and without OSMF group and comparison of trace elements with stages of OSMF was done by one-way ANOVA test.

RESULTS

All 200 individuals were matched with age and sex in both the groups. Out of the total 200 ears in group with OSMF, 61% of the ears showed normal hearing while 39% of the ears showed CHL. All of the total 200 ears showed normal hearing in without OSMF group.

[Table/Fig-3] provides the descriptive statistics of age and gender in both the group. The mean age in group without OSMF was 23.81±3.67 years with the range of 14-35 years. The distribution of individual ratio of male and female in both the groups was equal that is 95:5.

Group	Mean age (in years)	Male:female ratio
Without OSMF	23.81±3.67	95:5 (19:1)
OSMF	23.83±3.70	95:5 (19:1)

[Table/Fig-3]: Demographic data.

In the present study, comparison of hearing loss in terms of AB gap was done amongst both the group. In group with OSMF, mean level of hearing loss in decibels was 16.4 dB, whereas in group without OSMF, it was 13.02 dB. In both the group the results were statistically significant [Table/Fig-4].

Group	n	Mean	Std. Deviation	p-value
OSMF	100	16.43	3.28	0.001*
Without OSMF	100	13.02	1.41	

[Table/Fig-4]: Comparison of mean hearing loss (AB gap) in decibel with and without OSMF by unpaired t-test.
If p-value at 95% confidence interval is significant then, <0.05=significant

[Table/Fig-5] is showing the comparison of hearing loss with stages of OSMF in right and left ear. It was seen that in right ear in stage I of OSMF maximum number of patients (35) were having normal hearing. In stage II, OSMF there were 18 individuals with normal and no individuals with mild hearing loss.

Hearing status	Stages of OSMF			Chi-square value	p-value
	I	II	III		
Hearing status right ear					
Normal	35	18	9	20.677*	0.001*
Minimal	5	17	14		
Mild	2	0	0		
Hearing status left ear					
Normal	36	20	4	40.772	0.001*
Minimal	6	15	13		
Mild	0	0	6		

[Table/Fig-5]: Comparison of hearing loss with stages of OSMF in right and left ear by Chi-square test.
If p-value at 95% confidence interval is significant then, p<0.05=significant

Copper level in OSMF group with normal hearing was 103.44 mg/dL and with hearing loss was 97.46 mg/dL. Similarly, the zinc level in OSMF group with normal hearing, the mean was 78.93 mg/dL, and with hearing loss was 75.24 mg/dL. Iron level (Fe) with OSMF

individual with normal hearing was 84.05 mg/dL, and with hearing loss was 76.51 mg/dL which was statistically significant with p-value=0.001 [Table/Fig-6].

Trace elements	Hearing status	OSMF		p-value
		Mean	Std. Deviation	
Cu (mg/dL)	Normal	103.44	24.23	0.011
	Hearing loss	97.46	28.96	
Zn (mg/dL)	Normal	78.93	22.77	0.28
	Hearing loss	75.24	18.82	
Fe (mg/dL)	Normal	84.05	25.34	0.001*
	Hearing loss	76.51	20.88	

[Table/Fig-6]: Comparison of trace element with hearing loss in patients with OSMF.
The comparison is made by unpaired-t test
If p-value at 95% confidence interval is significant then, <0.05 =significant

[Table/Fig-7] is showing comparison of trace elements with stages of OSMF. Copper level was increased as stage increased and it was statistically significant. Whereas, zinc and iron levels were decreased as stage increased.

The OSMF is a slowly progressing condition in which "fibrous bands" grow in the "oral mucosa", limiting tongue movement severely. Degenerative alterations in the soft palate muscles, oedema, as well as atrophy of the palatal and paratubal muscles have all been observed by various authors [19]. The nasopharynx connects the ET to the middle ear chamber. Hearing loss occurs when the function of closure and opening is impaired [4]. The tensor veli palatine and levetor veli palatine muscles are linked to the soft palate. Some of the writers looked at the tissues of people with OSMF under a microscope and found dense "collagen bundles" that are directed and stretched into the underlying muscle, as well as muscle fibre degradation [15,18].

In present study, when the comparison of the serum trace elements was done between both groups, it was found that the level of Cu were statistically increased in OSMF group whereas the level of Zn and Fe gradually decreased in OSMF group in comparision to without OSMF group patients. In present study, association of trace elements with different stages of OSMF was also found. In the present study, a rise in serum Cu levels was seen and reduced

Trace elements	Stage of OSMF	n	Mean	Std. Deviation	Std. Error	95% Confidence interval for mean		F	Sig.
						Lower bound	Upper bound		
Cu (mg/dL)	I	42	80.10	13.08	2.02	76.02	84.18	80.495	0.001*
	II	35	104.61	16.47	2.78	98.96	110.27		
	III	23	133.36	20.89	4.36	124.32	142.39		
Zn (mg/dL)	I	42	81.04	23.28	3.59	73.79	88.30	1.531	0.221
	II	35	76.82	21.28	3.60	69.51	84.13		
	III	23	71.54	15.70	3.27	64.75	78.33		
Fe (mg/dL)	I	42	86.43	24.13	3.72	78.91	93.95	2.027	0.137
	II	35	77.25	24.35	4.12	68.89	85.62		
	III	23	76.28	20.86	4.35	67.26	85.30		
Post-hoc analysis for copper									
I			II			0.001*			
			III			0.001*			
II			III			0.001*			

[Table/Fig-7]: Comparison of trace elements with stages of OSMF by one-way ANOVA test.

DISCUSSION

The present study consisted of 100 patients without OSMF and 100 with OSMF, between 14-35 years of age. Males were predominated with 95% in both groups. Similar results were found by Lai DR et al., who reported 97.67% of male predilection [13]. Other studies on OSMF by Yeh CJ reported Males (M)-88.89%, Females (F)-11.11% and Hazarey VK et al., reported general male predilection as M- 90.91% F- 9.09% [14,15]. However, in contrast, the general female preponderance was found in OSMF group as reported by Haque MF et al., with F-62.07% M- 37.93% [16].

In the present study, comparison of hearing loss in different stages of OSMF had been done and it was found to be significant i.e., as the stage progressed the AB gap shifted from normal, that is suggestive of eustachian tube involvement. "Hearing loss" in right and left ear was found to be positively associated with OSMF stages I, II, and III in this investigation. The OSMF disease produced ear pain owing to Eustachian Tube (ET dysfunction and patency due to the involvement of surrounding muscles, resulting in mild to severe hearing loss. In "CHL", normal BC threshold and AC threshold decreases than normal threshold [17]. Results of present study were similar with earlier studies and showed that hearing loss was more in advanced condition of OSMF [3,9].

The percentage of normal hearing in OSMF individuals was 61% whereas the percentage of CHL was 39%. However, study done by Gupta SC et al., reported 72.2% showed normal hearing and mild to moderate CHL in 18% of individuals [18].

Zn and Fe levels were observed in serum as the stages increased. The elevated level of serum Cu in patients with OSMF could cause upregulation of lysyloxidase enzyme for crosslinking of collagen and elastin [20-22]. The findings of present study are in accordance with the previous studies done by Luquman M et al., Yadav A et al., Srilekha M [7,23,24].

When serum trace elements were compared with the level of hearing loss in OSMF individuals, increased levels of copper was found amongst OSMF group with normal hearing and in hearing loss, but it was not statistically significant. The reason for the increase in the level of Cu levels in the OSMF individuals was areca nut as it has high content of Cu and chewing areca nut releases Cu into the saliva regardless of normal or hearing loss [25]. So, in OSMF whether the hearing loss is present or not the Cu will always be increased. Similarly, decreased levels of Zn and Fe were found amongst OSMF group with normal hearing and in individuals with hearing loss. Though decreased amount of Zn and Fe were seen in OSMF group, it was statistically significant with Fe levels only.

While the cause of the decline in zinc and iron levels is similar for zinc levels, the Zn dependent superoxide dismutase is said to be an indicator of early mucosal changes preceding carcinogenesis [26]. This finding is in accordance with previous studies like those of Shettar SS [27]. However, decreased Fe levels in OSMF might be due to more use of iron in collagen synthesis leading to utilisation of Fe in collagen synthesis, epithelial vascularity declined. It causes burning sensation, erosion and fibrosis [3].

At present, detection of established carcinoma and progression of disease from premalignant to malignant relies heavily on histopathological examination. Recently much emphasis has been given towards recognition of trace elements in "oral cancer" and "precancerous" condition because of the encouraging result of the studies on head and neck carcinoma, lymphoma, lung and breast carcinoma [5].

The well known consequences and impact of OSMF on overall health leads to increased risk of developing hearing loss which subsequently would influence the quality of life. The results support the concept of determining the degree of OSMF and hearing loss with the levels of trace elements. Detection of trace elements in OSMF can open the doors for novel analytic and therapeutic modalities in areas of medicine and oncology. Thus, Eustachian tube functions may be affected in OSMF; hence individuals with OSMF should be screened for hearing loss.

Limitation(s)

The level of trace element, hearing status and OSMF were not recorded after treatment. It was a cross-sectional observational study. Long-term analysis is needed to determine the stability of results. Follow-up study of OSMF is also needed which may help and guide us further for considering trace elements as prognostic marker.

CONCLUSION(S)

Within the limitations of the study, there are significant association between grades of OSMF, hearing loss and levels of trace elements. As the OSMF stage progresses, the hearing impairment increases. One of the most serious side-effects of OSMF is hearing loss. All OSMF patients should be evaluated for hearing loss. Therefore, all OSMF patients should be referred to the ENT consultation for further treatment.

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