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Original Article

Assessment of anxiety, depression, and serum cortisol level in oral submucous fibrosis patients: A controlled clinical trial

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ABSTRACT

Objective: The aim of this study was to assess the anxiety, depression, and serum cortisol level in OSMF patients. **Materials and Methods:** This cross-sectional study was conducted in the Outpatient Department of Oral Medicine and Radiology, Teerthanker Mahaveer Dental College and Research Centre, Moradabad, Uttar Pradesh, India. Age- and gender-matched 105 patients were divided into three equal groups as follows: Group 1 – those with areca nut chewing habits and OSMF, Group 2 – those with areca nut chewing habits but no OSMF, and Group 3– those without areca nut chewing habits and without OSMF. Anxiety and depression were assessed by the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale, respectively. Serum cortisol level was also measured simultaneously. **Statistical Analysis:** Paired *t*-test, Chi-square test, and analysis of variance were used. **Results:** Fifty (47.62%) patients were observed to be in the age group of 25–32 years. Ninety-six (91.4%) patients were males and 9 (8.6%) were females. The mean serum cortisol level was observed to be higher among patients with OSMF-C followed by those with OSMF-D. **Conclusion:** We conclude that there is a significant association between OSMF, depression, and serum cortisol level.

Key words: Anxiety, depression, oral submucous fibrosis, serum cortisol

INTRODUCTION

Oral submucous fibrosis (OSMF) is a premalignant disease of oral mucosa. It predominantly occurs in Southeast Asia. It has also been found to occur in Europe and North America. The prevalence rate of OSMF in India has increased over the past few years from 0.03% to 6.42%. It is a chronic and progressive disease. The malignant transformation rate of OSMF into

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squamous cell carcinoma is as high as 7.6% over a 17-year period.[1-4]

OSMF is multifactorial in origin. The habit of chewing of commercially available areca nut product (pan masala) is the most important etiological agent of OSMF. The habit of chewing of raw areca nut is also associated with OSMF with a mean duration of 6–10 years. The areca nut alkaloid arecoline has been identified as the principal causative factor in the pathogenesis of OSMF. It increases fibroblast proliferation and collagen formation by increasing the production of growth factors (platelet-derived growth factor, fibroblast growth factor, transforming growth factor-beta, and connective tissue growth factor), cytokinins (interleukin-1 [IL-1], IL-6, IL-8, and tumor necrosis factor-alpha), tissue inhibitor of metalloproteinase and also by reducing the matrix metalloproteinase production and collagen phagocytosis. Areca nut has a high copper content. This acts as a mediator of OSMF by upregulating collagen production in oral fibroblasts. Genetic predisposition and nutritional deficiencies have also been implicated in the pathogenesis of OSMF.[5,6]

OSMF is characterized by juxtaepithelial inflammatory reaction and progressive fibrosis of the submucosal tissues such as lamina propria and deeper connective tissues. The oral epithelium overlying the fibrous condensation becomes atrophic in most cases.[7] The interrelationship between chronic physical illness and psychiatric morbidity is well established.[8-12]

There is a scarcity of literature on psychiatric morbidity in OSMF, and its association with serum cortisol level has not been studied. The aim of the present study was to assess the frequency of anxiety and depression and their association with serum cortisol level in patients with OSMF.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Outpatient Department of Oral Medicine and Radiology, Teerthanker Mahaveer Dental College and Research Centre, Moradabad, Uttar Pradesh, India, from June 2015 to May 2016. The protocol was approved by the institutional ethics committee. Written consent was obtained from each patient.

One hundred and five patients aged 18–40 years were enrolled for the study. They were categorized into three groups of 35 patients each, matched for age and gender as follows: Group 1 – those patients with areca nut chewing habit and OSMF, Group 2 – those with areca nut chewing habits without OSMF, and Group 3 – those without areca nut chewing habit and without OSMF. Group 1 was the study group (OSMF group). Group 2 and Group 3 formed the control group.

Patients with a history of psychiatric disorders, coexisting systemic diseases (cardiovascular diseases, asthma, chronic obstructive pulmonary disease, diabetes mellitus, arthritis, carcinoma, migraine, and HIV infection), oral mucosal disorders (burning mouth syndrome, oral lichen planus, and recurrent aphthous stomatitis), and miscellaneous diseases (temporomandibular joint disorders, facial neuralgia, atypical facial pain, atypical odontalgia, bruxism, salivary gland diseases, chronic advanced peridontitis, and viral infection) and pregnant women were excluded from the study.

Detailed clinical examination was carried out on all patients enrolled for the study. The identification of OSMF was made on the basis of history and characteristic clinical features (inability to open the mouth, intolerance to spicy food, altered mucosal appearance, tightening feeling, or firm fibrous bands in buccal and labial mucosa). Study group (OSMF group) patients were divided clinically into four subgroups (stages) based on the interincisal distance (ID): OSMF-A (ID >35 mm), OSMF-B (ID between 30 and 35 mm), OSMF-C (ID between 20 and 30 mm), and OSMF-D (ID <20 mm). OSMF-A represented the initial stage while OSMF-D the most advanced stage.

All the patients were assessed for severity of anxiety and depression by the Hamilton Anxiety Rating Scale (HAM-A) questionnaire and the Hamilton Depression Rating Scale (HAM-D) questionnaire, respectively, and the serum cortisol level was measured by enzyme-linked fluorescent assay (ELFA).

The HAM-A comprises 14 items (anxious mood, tension, fears, insomnia, intellectual, depressed mood, somatic complaints muscular, somatic complaints sensory, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, behavior at interview) and 5 responses (with scores 0, 1, 2, 3, and 4 indicating not present, mild, moderate, severe, very severe, respectively) to each item. A patient has to select one response (answer) for each item (question) and then the total score (range from 0 to 56) is calculated. A total score of >17 indicates

mild anxiety, 18–24 mild-to-moderate anxiety, and 25–30 moderate-to-severe anxiety.

The HAM-D comprises 17 items (depressed mood, feeling of guilt, suicide, insomnia early, insomnia middle, insomnia late, works and interests, retardation, agitation, anxiety psychic, anxiety somatic, somatic symptoms gastrointestinal, somatic symptoms general, genital symptoms, hypochondriasis, loss of weight, and insight) and 3–5 responses (with scores between 0 and 4) for each item. The interviewing clinician has to select one response (answer) for each item (question) and then the total score (range 0–52) is calculated. A total score of 0–7 indicates normal, 8–13 mild depression, 14–18 moderate depression, 19–22 severe depression, and ≥23 very severe depression.

The serum cortisol level of each patient was measured by MiniVidas analyzer (Bio Merieux S. A, Lyon, France) – a compact automated immunoassay system based on ELFA technique. The normal serum cortisol level ranges from 138 to 600 nmol/L (fasting 8 AM to 12 noon).

Statistical analysis

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) (Version 20.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 105 patients were studied. Fifty (47.62%) were observed to be in the age group of 25–32 years, of which 17 (16.19%), 16 (15.24%), and 17 (16.19%) patients belonged to Group 1, Group 2, and Group 3, respectively. Gender distribution of all patients revealed 96 (91.4%) males and 9 (8.6%) females. Group 1, Group 2, and Group 3 comprised of 32 (30.48%), 33 (31.43%), and 31 (29.53%) males and 3 (2.86%), 2 (1.90%), and 4 (3.80%) females, respectively.

Mild anxiety was observed in 29 (27.62%), 34 (32.38%), and 33 (31.43%) individuals and moderate anxiety in 6 (05.72%), 1 (00.95%), and 2 (01.90%) individuals in Group 1, Group 2, and Group 3, respectively. None of them had severe anxiety. Statistical analysis revealed that the values (χ^2 = 5.104, P = 0.078) were not statistically significant [Table 1].

Mild, moderate, severe, and very severe depression were observed in 17 (16.20%), 1 (0.95%), 1 (0.95%), and 1 (0.95%) Group 1 subjects, respectively. In Group 2, 14 (13.33%) had mild depression and 3 (2.85%) had moderate depression, while Group 3 had 9 (6.57%) subjects suffering from mild depression. Statistical analysis revealed that the values (χ^2 = 13.24, P = 0.104) were not statistically significant [Table 2].

Twenty-eight (26.67%) subjects had normal serum cortisol level and 7 (6.67%) had elevated serum cortisol level in Group 1. Thirty-four (32.38%) subjects had normal serum cortisol level, while 1 (0.95%) had elevated serum cortisol level in Group 2. Normal serum cortisol level was observed in all cases of Group 3. Statistical analysis revealed that the values (χ^2 = 11.76, P = 0.03) were statistically highly significant [Table 3].

Analysis of variance of HAM-A score, HAM-D score, and serum cortisol level among study and control groups revealed the mean HAM-A score to be statistically significant ($P < 0.05$), the mean HAM-D score to be statistically insignificant ($P > 0.05$), and the mean serum cortisol level to be statistically significant ($P < 0.05$) [Table 4].

Table 1: Assessment of severity of anxiety by Hamilton Anxiety Rating Scale among patients of different groups

Group	Mild anxiety, *n* (%)	Moderate anxiety, *n* (%)	Severe anxiety, *n* (%)
Group 1	29 (27.62)	6 (5.72)	0
Group 2	34 (32.38)	1 (0.95)	0
Group 3	33 (31.43)	2 (1.90)	0
Total	96 (91.43)	9 (8.57)	0

χ^2=5.104, P=0.078, not statistically significant

Table 2: Assessment of severity of depression by Hamilton Depression Rating Scale among patients of different groups (*n*=105)

Group	Normal, *n* (%)	Mild depression, *n* (%)	Moderate depression, *n* (%)	Severe depression, *n* (%)	Very severe depression, *n* (%)
Group 1	15 (14.29)	17 (16.20)	1 (0.95)	1 (0.95)	1 (0.95)
Group 2	18 (17.14)	14 (13.33)	3 (2.85)	0	0
Group 3	26 (24.77)	9 (6.57)	0	0	0
Total	59 (56.20)	40 (38.10)	4 (3.80)	1 (0.95)	1 (0.95)

χ^2=13.24, P=0.104, not statistically significant

Comparison of mean HAM-A score, HAM-D score, and serum cortisol level among OSMF-A, OSMF-B, OSMF-C, and OSMF-D subgroups of Group 1 with control group revealed an increase in mean HAM-A score from OSMF-A to OSMF-D, increase in mean HAM-D score from OSMF-A to OSMF-C which was equal to OSMF-D. The mean serum cortisol level was observed to be maximum in OSMF-C followed in descending order by OSMF-D, OSMF-B, and OSMF-A. The ratio of serum cortisol level in OSMF-C to control group was noted to be 1.89:1. The logistic regression analysis with serum cortisol as dependent and HAM-A score, HAM-D score, and OSMF stage of study group as independent factors revealed that HAM-D and OSMF stage had a significant association with the serum cortisol level [Table 5]. The flowchart of the study participants is presented in Figure 1.

Table 3: Assessment of serum cortisol level (nmol/L) among patients of different groups

Group	Normal level (138-600 nmol/L), *n* (%)	Elevated level, *n* (%)
Group 1	28 (26.67)	7 (6.67)
Group 2	24 (32.38)	1 (0.95)
Group 3	35 (33.33)	0
Total	97 (92.38)	8 (7.62)

χ^2=11.76, *P*=0.03, highly significant

DISCUSSION

In the present study, the mean anxiety score of the study group showed a highly significant difference ($P < 0.05$) from the control, the mean score of depression was found to higher in the study group as compared to the control group, the difference of which was not

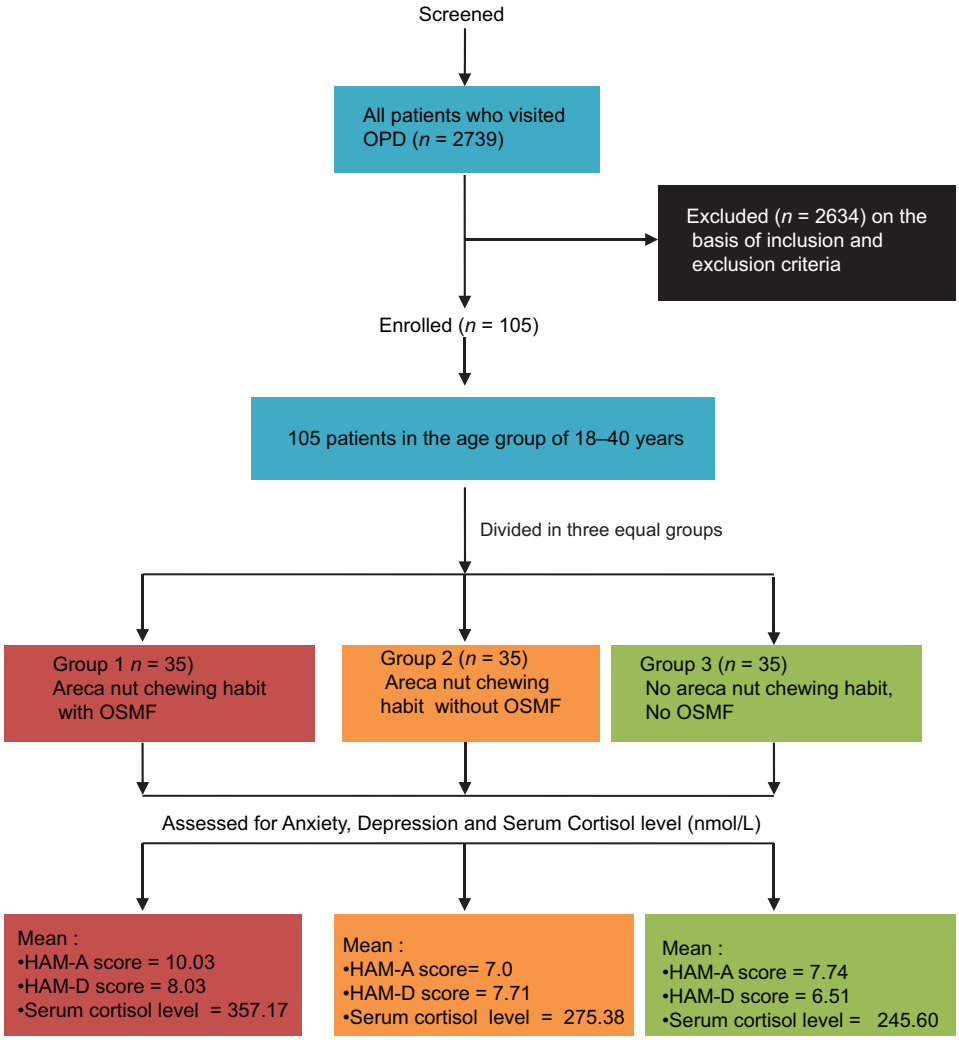

Figure 1: Flowchart of the study participants. N: Number of patients, OSMF: Oral submucous fibrosis, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, nmol/L: nanomoles per liter

Table 4: Analysis of variance of Hamilton Anxiety Rating Scale score, Hamilton Depression Rating Scale score, and serum cortisol level among patients of different groups (*n*=105)

	Patients of different groups (mean±SD)				Significance (ANOVA)	
	Group 1	Group 2	Group 3	Total	*F*	*P*
HAM-A score	10.03±5.16	7±4.37	7.74±4.25	8.26±4.75	4.103	0.019
HAM-D score	8.03±4.73	7.71±4.07	6.51±2.79	7.42±3.96	1.435	0.243
Serum cortisol level	357.17±270.98	275.38±140.03	245.60±191.82	292.71±191.82	3.314	0.040

ANOVA: Analysis of variance, SD: Standard deviation, HAM-D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale

Table 5: Comparison of mean (standard deviation) of Hamilton Anxiety Rating Scale score, Hamilton Depression Rating Scale score, and serum cortisol level (nmol/L) among patients of study group (OSMF-A to OMSF-D) and control group

Group	Mean±SD		
	HAM-A score	HAM-D score	Serum cortisol level
OSMF-A	4.29±1.39	3.86±0.89	123.42±133.86
OSMF-B	7.71±3.86	5.86±4.67	234.92±224.69
OSMF-C	12±4.4	10±3.82	494.63±275.41
OSMF-D	13.5±4.45	10.3±5.06	455.07±244.41
Control group	7.37±4.29	7.11±3.52	260.61±126.99
Total	8.26±4.75	7.42±3.96	292.71±191.82

SD: Standard deviation, OSMF: Oral submucous fibrosis, HAM-D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale

statistically significant ($P > 0.05$), and the mean serum cortisol level of the study group showed a highly significant difference ($P < 0.05$) from the control.

The present study observed a close connection between depression, serum cortisol, and OSMF. Progression of OSMF stage has been noted to be associated with depression probably because of chronicity of the condition and critical weakening (restricted mouth opening, eating, gulping, talking troubles, and smoldering sensation in the mouth), which consequently affected the serum cortisol level. Depression has an effect on the hypothalamo–pitutary–adrenal axis, leading to increased production of corticotrophin-releasing hormone and consequently increase in the serum cortisol level.

OSMF and its association with psychiatric morbidity have been noticed by Mubeen *et al*., Raja *et al*., and Arjun *et al*. Advanced OSMF stages have been reported to be associated with higher psychiatric morbidity by Mubeen *et al*. and Raja *et al*.[13-15]

The observations of the present study are in accordance with those of the previously reported studies mentioned above with regard to the association of OSMF and psychiatric morbidity and their relation to advanced OSMF staging. Over and above, the present study has added further light on these relationships by correlating them with serum cortisol level as anxiety, depression, and serum cortisol level were observed to be higher among patients with advanced OSMF stage as compared with the control.

CONCLUSION

We conclude that there is an association between anxiety, depression, serum cortisol level, and OSMF and all are interlinked with each other. Further studies are needed to address neuroendocrinal abnormalities among patients with OSMF.

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Conflicts of interest

There are no conflicts of interest.

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