

# Assessment and correlation of anxiety, depression and serum cortisol levels in patients with oral submucous fibrosis and leukoplakia: A clinicohematological study

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## Abstract

**Context:** Potentially malignant disorders (PMDs) of the oral cavity like oral submucous fibrosis (OSMF) and leukoplakia are known to be caused due to addictive habits, while serum cortisol is accepted to be a stress hormone.

**Aim:** The present study was aimed to assess and correlate the anxiety, depression and serum cortisol levels in habit-associated PMDs such as OSMF and leukoplakia and compare it with healthy subjects.

**Materials and Methods:** Ninety patients were included in the study and were divided into three Groups, namely Group I (OSMF), Group II (leukoplakia) and Group III (control group). Serum cortisol levels and severity of anxiety and depression using the Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) were recorded and correlated.

**Results:** A significant correlation existed between serum cortisol level and levels of both anxiety and depression between Group I and II as compared to the control group.

**Conclusion:** There exists a definite correlation between serum cortisol levels and the levels of anxiety and depression in patients with leukoplakia and OSMF, with increasing levels of serum cortisol and higher values in both the HAM-A and HAM-D scales in patients with both OSMF and leukoplakia. PMDs such as leukoplakia and OSMF have an established cancer-causing potential. Anxiety and depression although prevalent are underdiagnosed and poorly understood. Hence, a holistic approach in the treatment of such pathologies including hematological investigations and psychological evaluation should be mandatorily made a part of the workup and treatment plan.

**Keywords:** Anxiety, depression, leukoplakia, oral submucous fibrosis, serum cortisol

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## INTRODUCTION

Stress is a feeling of emotional or physical tension, which manifests itself as somatic and/or psychological symptoms such as lethargy, insomnia, anxiety and/or depression. Anxiety can be defined as “an emotional state, characterized by uneasiness, discomfort and fear about some defined or undefined threat” while depression is “a state of unhappiness or sadness,” which is experienced from time to time.<sup>[1]</sup> Stress utilizes two mechanisms to deteriorate our immune system, thereby facilitating a disease process. The first is a biological mechanism, which is mediated through the “hypothalamic–pituitary–adrenal (HPA) axis” and the production of “cortisol.” The second is the behavioral mechanism which promotes poor health behavior such as smoking, alcoholism, unhealthy diet, poor oral hygiene habits and para functional habits. This results in a deterioration of oral health as a response to these habits and causes a variety of oral diseases.<sup>[1]</sup> In the course of time, people develop habits including consumption of gutka, tobacco, betel nut chewing, pan chewing and smoking, leading to the development of potentially malignant disorders (PMDs).

Oral submucous fibrosis (OSMF) and leukoplakia are some of the most common oral mucosal diseases in human beings and constitute entities that deserve to be investigated as psychosomatic diseases. It has been stated that up to 40% of cancer patients suffer from a significant level of distress. Cortisol also known as the “stress hormone” has been used as an indicator in stress evaluation. Cortisol is the major glucocorticoid in humans and has influences on metabolism, immunoregulation, vascular responsiveness, cognition and behavior.<sup>[2]</sup> In recent years, the important relationship between chronic physical illnesses and psychiatric disorders has been studied extensively. However, literature on psychiatric morbidity in OSMF and leukoplakia remains scarce.<sup>[3]</sup> The aim of the study was to estimate and correlate levels of anxiety, depression and serum cortisol in patients with OSMF and leukoplakia, thereby establishing a significant clinicohematological relation.

## MATERIALS AND METHODS

The study included patients reporting to the institutional outpatient department. 90 patients between 20 and 45 years of age were included and assigned to the 3 groups of 30 patients each:

- Group I – 30 patients with clinically and histopathologically proven OSMF [Figure 1]
- Group II – 30 patients with clinically and histopathologically proven leukoplakia [Figure 2]



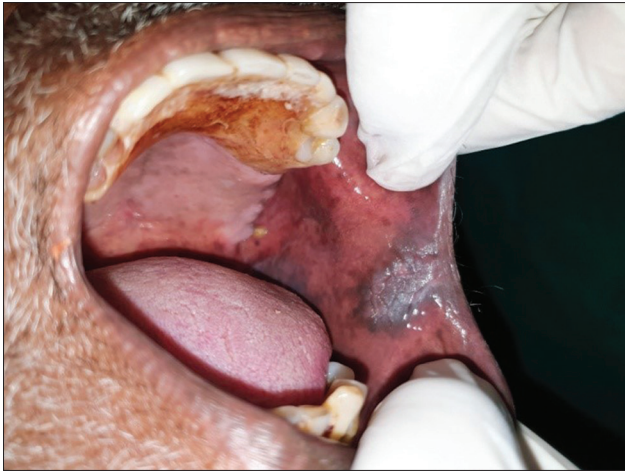
**Figure 1:** Patient with oral submucous fibrosis and reduced mouth opening

- Group III – 30 age- and sex-matched healthy controls without any signs and symptoms of the above-mentioned diseases.

Patients were included for the study based on the following inclusion criteria of patients being willing for the study, patients above 18 years of age with a definite history of habits of smoking and smokeless tobacco with by-products of tobacco and areca nut chewing were included. PMDs of clinically and histopathologically diagnosed OSMF and Leukoplakia. The exclusion criteria of the study were patients unwilling for the study and patients with ongoing treatment of either of the included diseases. Individuals with physiological conditions such as pregnancy or systemic diseases and medically compromised patients including psychiatric disorders. Patients with oral mucosal disorders and periodontal diseases.

A detailed case history recording symptoms and history of habits was recorded. The patients were examined under standard examination settings. Hamilton Anxiety Rating Scale (HAM-A) questionnaire and Hamilton Depression Rating Scale (HAM-D) questionnaire were recorded in the presence of a psychiatrist.

The HAM-A scale<sup>[4]</sup> comprised 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 and behavior at interview) and 5 responses (with scores 0, 1, 2, 3 and 4 indicating not present, mild, moderate, severe and very severe, respectively) to each item. The patient selected one response (answer) for each item (question) after which the total score (range from 0 to 56) was calculated.



**Figure 2:** Patient with leukoplakia of the left labial mucosa

The HAM-D scale<sup>[5]</sup> comprised 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 had to select one response (answer) for each item (question) and then the total score (range 0–52) was calculated.

All the patients were scheduled for blood analysis for cortisol levels in the morning. Standard aseptic protocol was followed and 5 ml of venous blood was drawn and all the samples were analyzed immediately. The serum cortisol level was estimated using electrochemiluminescence immunoassay ROCHE COBA E 411. The accepted normal serum cortisol level ranged from 138 to 600 nmol/L. The study was approved by the institutional ethical committee and required informed consents were also obtained from the participants of the study.

### Statistical analysis

The data collected were tabulated using Microsoft excel. The data were analyzed using Statistical package for Social Sciences (SPSS) for Windows, version 25.0. (Armonk, NY: IBM Corp). Descriptive statistics such as mean, standard deviation and percentage were used. The Shapiro–Wilk test was used for assessing the normality of distribution of all parameters. Comparison of variables between two groups with normal distribution was carried out using independent samples *t*-test. Comparison of means of more than two groups was carried out using one-way analysis of variance with *post hoc* Tukey's HSD for data meeting the assumption of homogeneity of variances and *post hoc* Games–Howell

test for data violating the assumption of homogeneity of variances. Chi-square or Fisher's Freeman–Halton Exact tests by cross-tabulation were applied to compare frequencies. Spearman's rank correlation was used to assess strength and direction of association between depression level and anxiety level with serum cortisol levels.  $P < 0.05$  was considered statistically significant.

### RESULTS

This study was conducted to determine the levels of anxiety, levels of depression and serum cortisol level in OSMF and leukoplakia patients. After analyzing the tabulated data, the following results were obtained.

Of the included study patients, the mean age calculated was  $33.56 \pm 6.45$  years; more males were diagnosed with both diseases than females. Gender distribution of patients showed that 81 (90%) were male and 9 (10%) were female. Of the enrolled patients, 60% had tobacco-related habits. Of all the recorded habits, 29 (48.3%) patients consumed gutkha or betelnut, 21 (35%) patients reported a cigarette smoking habit and only 10 (16.7%) patients reported smoking beedis (locally made cigarettes).

Distribution of study subjects according to the level of anxiety by HAM-A scale revealed that 22 (24.4%) patients had normal anxiety, 43 (47.8%) patients had mild anxiety and 25 (27.8%) had moderate anxiety. None of them had severe anxiety. Upon correlation, the mean serum cortisol level in patients with normal anxiety was  $167.73 \pm 30.55$  nmol/L, mild anxiety was  $350.18 \pm 94.02$  nmol/L and moderate anxiety was  $478.55 \pm 86.81$  nmol/L and was statistically significant with  $P = 0.0001$  [Table 1].

Among patients reporting normal anxiety levels, 22 (100%) were from Group III. Among patients suffering from mild anxiety, 15 (34.9%) were from Group I, 20 (46.5%) were from Group II and only 8 (18.6%) were from Group III. 15 (60%) patients with moderate anxiety levels were from Group I, while the remaining were from Group II, which was statistically significant with  $P = 0.001$  [Table 2]. The mean anxiety score was  $18.30 \pm 3.31$  in Group I,  $17.73 \pm 3.38$  in Group II and  $7.60 \pm 4.56$  in Group III, which was statistically significant with  $P = 0.0001$  [Table 3].

### Comparison of depression levels among study groups

Distribution of study subjects according to the level of depression by HAM-D scale revealed that 38 (42.3%) patients were recorded to have normal levels of depression, 25 (27.8%) patients had mild depression, 22 (24.4%) patients



had moderate depression, 3 (3.3%) had severe depression and 2 (2.2%) patients had very severe depression. The mean cortisol level was highest in patients with greater levels of depression and this result was statistically significant with  $P = 0.0001$  [Table 4]. Of all the patients, a majority of patients with normal levels of depression (71.1%) were from the control group, while a majority of patients with mild depression (52%) were from Group II. Patients with moderate and very severe depression were equally distributed between Group I and II, while patients with severe depression (66.7%) were from Group II [Table 5]. The mean depression score was significantly increased in Group I and II with  $P = 0.0001$  [Table 6].

**Table 1: Comparison of serum cortisol level according to anxiety levels**

Anxiety levels	n	Mean serum cortisol level (nmol/L), mean±SD	One-way ANOVA	
			P	Significance
Normal	22	167.73±30.55 <sup>a</sup>	0.0001	Significant
Mild	43	350.18±94.02 <sup>a</sup>		
Moderate	25	478.55±86.81 <sup>a</sup>		

<sup>a</sup>Games-Howell *post hoc* analysis, statistically significant at  $P < 0.05$ . SD: Standard deviation

**Table 2: Comparison of anxiety levels among study subjects of all the groups**

Group	Anxiety level			P	$\chi^2$ Significance
	Normal, n (%)	Mild, n (%)	Moderate, n (%)		
Group I (OSMF)	0	15 (34.9)	15 (60.0)	0.001	Significant
Group II (leukoplakia)	0	20 (46.5)	10 (40.0)		
Group III (control)	22 (100.0)	8 (18.6)	0		
Total	22 (100.0)	43 (100)	25 (100.0)		

OSMF: Oral submucous fibrosis

**Table 3: Comparison of mean anxiety score among study subjects of all the groups**

Groups	n	Mean anxiety score (mean±SD)	One-way ANOVA	
			P	Significance
Group I (OSMF)	30	18.30±3.31 <sup>a</sup>	0.0001	Significant
Group II (leukoplakia)	30	17.73±3.38 <sup>b</sup>		
Group III (control)	30	7.60±4.56 <sup>ab</sup>		

<sup>ab</sup>Tukey HDS *post hoc* analysis, statistically significant at  $P < 0.05$ . SD: Standard deviation, OSMF: Oral submucous fibrosis

**Table 4: Comparison of serum cortisol level according to depression levels**

Depression levels	n	Mean serum cortisol level (nmol/L), mean±SD	One-way ANOVA	
			P	Significance
Normal	38	226.97±82.50 <sup>abcde</sup>	0.0001	Significant
Mild	25	362.44±74.45 <sup>abcde</sup>		
Moderate	22	462.05±92.56 <sup>abcde</sup>		
Severe	3	512.18±101.14 <sup>abd</sup>		
Very severe	2	662.06±39.01 <sup>abcde</sup>		

<sup>abcde</sup>Tukey HDS *post hoc* analysis, statistically significant at  $P < 0.05$ . SD: Standard deviation

### Comparison of serum cortisol level among study groups

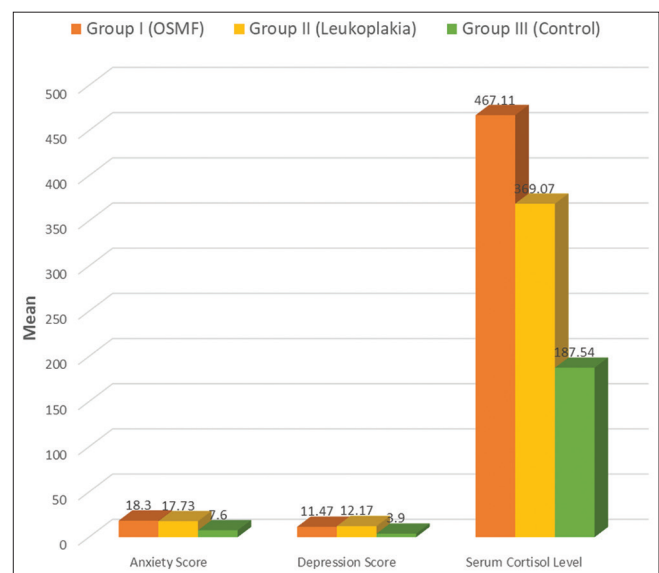
The mean serum cortisol level was highest in Group I (418.09 ± 100.11 nmol/L) and least in Group III (187.54 ± 43.32 nmol/L). This finding was statistically significant with  $P = 0.0001$  [Table 6]. Serum cortisol levels were also significantly higher in tobacco users [Table 7].

### Correlation of serum cortisol levels with anxiety and depression

A very high statistically significant strong positive correlation was found between anxiety, depression and serum cortisol levels [Table 8]. The mean anxiety score was found to be significantly higher in Group I (18.30 ± 3.31) and Group II (17.73 ± 3.38) when compared to Group III (7.60 ± 4.56). Similarly, the mean depression score was significantly higher among the same groups. Comparison of mean serum cortisol level between three groups showed significantly high mean serum cortisol levels in Group I (467.11 ± 93.89) and Group II (369.07 ± 81.24) when compared to controls (187.54 ± 43.33) [Tables 3 and 6 and Graph 1].

## DISCUSSION

Cortisol is a vital catabolic hormone produced by the adrenal cortex of the kidney and is released in a diurnal fashion, with blood levels peaking in the morning to facilitate arousal and steadily declining thereafter. Cortisol is a key player in stress response. In the presence of a physical or psychological threat, cortisol levels surge to provide the energy and substrate necessary to cope with stress provoking stimuli or escape from



**Graph 1: Comparison of mean anxiety score mean depression score and mean serum cortisol level among all the groups**

**Table 5: Comparison of depression levels and mean depression score among study subjects of all the groups**

Group	Depression level					Fisher Freeman Halton exact test	
	Normal, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Very severe, n (%)	P	Significance
Group I (OSMF)	8 (21.0)	9 (36.0)	11 (50.0)	1 (33.3)	1 (50.0)	0.001	Significant
Group II (leukoplakia)	3 (7.9)	13 (52.0)	11 (50.0)	2 (66.7)	1 (50.0)		
Group III (control)	27 (71.1)	3 (12.0)	0	0	0		
Total	38 (100.0)	25 (100.0)	22 (100.0)	3 (100.0)	2 (100.0)		

OSMF: Oral submucous fibrosis

**Table 6: Comparison of mean depression score and mean serum cortisol levels among the study subjects of all the groups**

Groups	n	Mean±SD		One-way ANOVA	
		Mean depression score	Mean serum cortisol level (nmol/L)	P	Significance
Group I (OSMF)	30	11.47±5.34 <sup>a</sup>	467.11±93.89 <sup>a</sup>	0.0001	Significant
Group II (leukoplakia)	30	12.17±3.72 <sup>a</sup>	369.07±81.24 <sup>a</sup>		
Group III (control)	30	3.90±2.16 <sup>ab</sup>	187.54±43.33 <sup>a</sup>		

<sup>ab</sup>Games-Howell *post hoc* analysis, statistically significant at  $P < 0.05$ .

SD: Standard deviation, OSMF: Oral submucous fibrosis

**Table 7: Comparison of serum cortisol level among tobacco users and nonusers**

Tobacco	n	Mean serum cortisol level (nmol/L), mean±SD	Independent sample t-test	
			P	Significance
Users	60	418.09±100.11	0.0001	Significant
Nonusers	30	187.54±43.32		

SD: Standard deviation

**Table 8: Correlation between serum cortisol levels and anxiety and depression**

Variables	n	Serum cortisol
Anxiety	Correlation coefficient	0.837*
	Significance (two-tailed)	0.0001
	n	90
Depression	Correlation coefficient	0.784*
	Significance (two-tailed)	0.0001
	N	90

\*Correlation is significant at 0.01 level

danger. However, although a stress-induced increase in cortisol secretion is adaptive in the short term, excessive or prolonged cortisol secretion may have crippling effects, both physically and psychologically.<sup>[6]</sup> In stressful situations, there is an activation of the HPA axis causing the release of cortisol, a hormone which shows a complex action on the metabolism of carbohydrates, proteins and lipids, besides acting on inflammatory and immunological responses and has been used as an evaluator of stress in many studies. Stress is considered one of the main etiological factors in many diseases.<sup>[7]</sup> It has been established with reasonable certainty that both physical and mental stress were related to an increase in cortisol levels. The interrelationship between chronic illness and psychiatric morbidity is also well established.<sup>[2]</sup>

In the present study, a majority of Group I (OSMF) had mild and moderate anxiety, which is in accordance with the study conducted by Kanodia *et al.*,<sup>[3]</sup> where a majority of OSMF patients had mild anxiety. There have been no studies conducted, reporting levels of anxiety in patients with leukoplakia. The present study recorded mild anxiety levels and higher mean anxiety scores in patients with leukoplakia when compared with the controls, while patients with OSMF had the highest mean anxiety scores of the 3 Groups. Our study reported very few patients with severe and very severe depression, which is again similar to a previous report.<sup>[3]</sup>

The mean cortisol levels were highest in patients with very severe depression. Group I had increased mean depression scores when compared to the control group. In the present study, Group II or patients with leukoplakia showed the highest intergroup mean depression score. Depression levels in patients with leukoplakia have not been reported for comparisons if any, with the current study.

A very high statistically significant and strong positive correlation was found between anxiety, depression and serum cortisol levels in patients with OSMF and leukoplakia. Such a relationship between increased depression with a concomitant increase in serum cortisol levels has been documented.<sup>[8]</sup> The increased depression and anxiety levels could be multifactorial and also be associated with symptoms of OSMF such as restricted mouth opening, inability to eat or chew various foods and speech problems. Substantiation of this requires more specific and detailed psychiatric evaluations. It could also result due to a stimulatory effect of depression on the hypothalamus pituitary adrenal axis, which increases the production of corticotropin-releasing hormone, leading to increase in serum cortisol level. Any disclosure of information regarding the presence of a PMD could itself result in anxiety and depression and requires further investigation to substantiate the same. It has been reported that psychiatric morbidity was found to be increased in patients with advanced stages of disease and up to moderate level of depression was seen in a majority of patients with OSMF.<sup>[9,10]</sup> This is similar to the present study where a strong association was found between psychiatric morbidity and advanced stages of OSMF and leukoplakia.

Present lifestyle patterns exhibit addictive habits to deleterious substances such as smoking, consumption of gutkha and tobacco and the frequency of these habits may increase with a concomitant increase in stress, which also increases the prevalence of PMDs.<sup>[11]</sup> It may therefore be said with reasonable certainty that an assessment of psychiatric morbidity would reflect the patients mental state, while the estimated levels of serum cortisol would indicate the stress pattern in these diseases. Both of these parameters could help in both early diagnosis and possible prevention of a life-threatening disease such as cancer. Hence, apart from diagnosis of these diseases, required psychological counseling should also be mandatorily added in the treatment regime.

## CONCLUSION

The findings from our study revealed that there is a strong association between psychiatric morbidity like anxiety, depression, in patients with advance stages of OSMF and leukoplakia with a similar increase in serum cortisol levels. These levels also positively correlated with advanced stages of disease. It can therefore be concluded that there exists a strong positive correlation between serum cortisol level, anxiety level and depression level in patients with habit-oriented diseases like OSMF and leukoplakia. Till date, there have been no such studies in patients with leukoplakia, which is a prevalent PMD in India. Further studies with larger sample sizes would help in the correlation of other neuroendocrinal abnormalities among patients with other PMDs.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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