



INTER-RELATIONSHIP BETWEEN STRESS AND SERUM CORTISOL LEVELS IN LEUKOPLAKIA AND ORAL SUBMUCOUS FIBROSIS: TIME TO DELIBERATE.

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ABSTRACT

Introduction: Stress, a blend of emotional and physical tension, triggers somatic and psychological symptoms like lethargy, insomnia, anxiety, and depression. It weakens immunity via two routes: the biological mechanism, involving the "hypothalamic-pituitary-adrenal (HPA) axis" and cortisol production, and the behavioural mechanism, fostering unhealthy habits such as smoking, alcoholism, and poor diet. Over time, these habits escalate, leading to potentially malignant disorders. **Aims:** To assess and establish the relationship between anxiety, depression, and serum cortisol levels, and to examine the levels of anxiety, depression, and serum cortisol in habit-associated potentially malignant disorders (PMDs) such as oral submucous fibrosis (OSMF) and leukoplakia, comparing them with those of healthy individuals. **Materials And Methods:** Our study group comprised of 60 participants in which 20 were of Leukoplakia, 20 OSMF and 20 healthy individuals. Selection was contingent upon clinical diagnosis. Assessments utilising the HAM-A and HAM-D questionnaires were conducted. Additionally, morning blood samples were collected from all participants for serum cortisol analysis. **Result:** We found a positive correlation between serum cortisol, anxiety and depression as compared to healthy controls when data was analyzed and tabulated using student 't' test and P value < 0.05 was considered to be statistically significant. **Conclusion:** In habit oriented patients there is a high probability of anxiety and depression. Also patients with anxiety and depression are more likely to start a habit of smoking or tobacco chewing. Through this study a positive correlation between both PMD and stress was assessed when compared with healthy controls

KEYWORDS : Cortisol, Potentially Malignant Disorder, Hamilton Anxiety rating scale, Hamilton depression rating scale.

INTRODUCTION

Stress is a condition characterized by emotional or physical strain, leading to symptoms like fatigue, sleep problems, anxiety, or depression, affecting both the body and mind. Anxiety is an emotional state marked by feelings of unease, discomfort, and fear related to a known or unknown threat. On the other hand, depression is a state of persistent unhappiness or sadness that can occur periodically [1].

Due to recent advances in health sciences, there has been heightened awareness among both the general population and healthcare professionals regarding the importance of oral health. Similar to systemic diseases, oral diseases have multifactorial causes, with stress often being a significant contributing factor [2].

Stress is believed to impact our immune system and contribute to the disease process through two mechanisms. One is the biological pathway involving the hypothalamic-pituitary-adrenal (HPA) axis and the production of cortisol. The other is a behavioural mechanism that encourages unhealthy habits such as smoking, alcohol consumption, poor dietary choices, inadequate oral hygiene practices, and para functional habits. These behaviors contribute to the deterioration of oral health in patients, leading to various oral diseases [2,3].

Over time, individuals develop habits such as consuming gutka, tobacco, betel nut chewing, pan chewing, and smoking. These habits can lead to the development of potentially malignant disorders (PMDs) [1]. Certain illnesses are classified as idiopathic, which means that their diagnosis and course of therapy are invariably debatable. Oral lichen planus (OLP), oral submucous fibrosis (OSMF), leukoplakia, squamous cell carcinoma (SCC) are the most common oral mucosal diseases are conditions that are recognized to humans and are worthy of further study as psychosomatic disorders. [4]

Oral leukoplakia is characterised by the appearance of white patches or plaques in the oral cavity. This condition is considered potentially malignant and is closely linked with tobacco use. [5]. The purpose of this study is to analyse the correlation between increased cortisol levels in the blood along with the anxiety, depression.

MATERIALS AND METHODS

The Study involved participants who presented at the institutional outpatient department. A total of 60 patients aged between 20 and 45

years were divided into three groups, each consisting of 20 patients.

Group I – 20 patients with clinically and proven Leukoplakia
Group II – 20 patients with clinically and proven OSMF
Group III – 20 Healthy controls

Inclusion Criteria:

Willingness to participate, age above 18 years, and a confirmed history of smoking, smokeless tobacco use, or areca nut chewing.

Exclusion Criteria:

Unwillingness to participate, ongoing treatment for the aforementioned diseases, physiological conditions like pregnancy or systemic illnesses, medically compromised states including psychiatric disorders, and patients with oral mucosal disorders or periodontal diseases.

A comprehensive case history was documented, detailing symptoms and habits. Patients underwent examination in a standardised setting. Additionally, assessments using the Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) were conducted [7,8].

The HAM-A scale consists of 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. Each item has 5 responses scored from 0 to 4

Scoring Response:

0- not present
1- mild
2- moderate
3- severe
4- very severe

The patient selects one response for each item, and the total score, ranging from 0 to 56, is then calculated.

The HAM-D scale consists of 17 items: depressed mood, feelings of guilt, suicide, early insomnia, middle insomnia, late insomnia, work

and interests, retardation, agitation, psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, weight loss, insight, hypochondriasis, genital symptoms, and general somatic symptoms. Each item has 3 to 5 responses, with scores ranging from 0 to 4.

The interviewing clinician selected one response for each item, and the total score, ranging from 0 to 52, was calculated.

All patients were scheduled for morning blood analysis to measure cortisol levels. Following standard aseptic protocol, 5 ml of venous blood was drawn, and the samples were analysed immediately. Serum cortisol levels were estimated using the electrochemiluminescence immunoassay ROCHE COBA E 411, with normal levels ranging from 138 to 600 nmol/L. The institutional ethical committee accepted the study, and each participant gave their informed consent.

Statistical Analysis

Microsoft Excel was utilized for the collection and tabulation of data. There was usage of descriptive statistics like mean, standard deviation, and percentage. Comparisons of variables between two groups with normal distribution were performed using an student-test. A p-value of less than 0.05 was considered statistically significant.

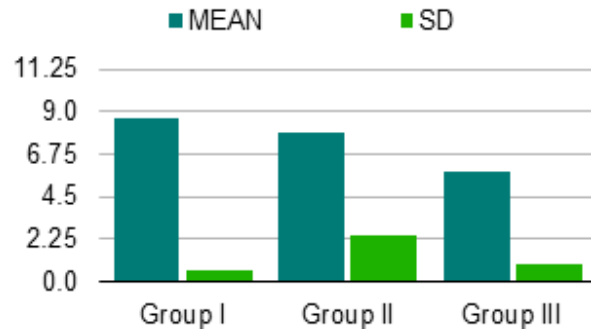
RESULTS

The study was conducted to determine and compare the levels of Serum Cortisol, Anxiety and Depression in Leukoplakia, OSMF and normal controls. After analyzing the tabulated data, following inference was concluded.

Mean age calculated in group I (leukoplakia) was 43.1 year, Group II (OSMF) was 41.8 year and group III (control) was 38.8 year respectively. Male female ratio in group I and II was 3:2 and in group III it was 1:1. Distribution of data of SCL compared between three groups it was observed that the mean with standard deviation between group I & II was 8.68 ±0.593 which was not statistically significant. However, mean and SD between group I & III and group II & III was 7.89 ±2.417 and 5.78 ±0.887 which was found to be extremely significant (Table:1 and Graph:1).

Table – 1 Comparison Of Serum Cortisol Level Among Study Groups

Groups	n	MEAN	SD	P VALUE	Significance
I	20	8.68	0.593±	0.16	Not Significant
II	20	7.89	2.417±	0.0001	Extremely Significant
III	20	5.78	0.887±	0.0001	Extremely significant



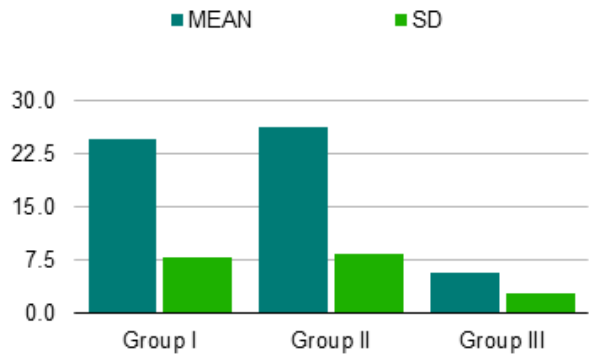
Graph 1 Comparison Of Serum Cortisol Level Among Study Groups

When anxiety levels using HAM-A scale were compared between three groups, the mean and SD in group I was 24.7±7.921 and the p. value of 0.53 was not statistically significant. Mean and SD in group II & III was 26.3±8.423 and 5.7±2.87 and p value calculated was 0.0001 which was extremely significant. (Table:2 and Graph:2).

Table 2 Comparison Of Anxiety Levels Among Study Groups

GROUPS	n	MEAN	SD	P VALUE	Significance
I	20	24.7	7.921±	0.53	Not Significant
II	20	26.3	8.423±	0.0001	Extremely Significant
III	20	5.7	2.867±	0.0001	Ext. significant

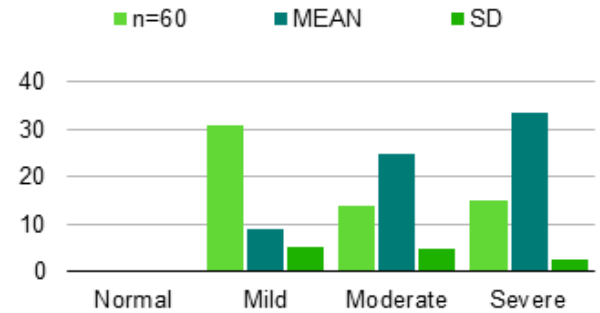
Similarly, the depression levels using HAM-D scale, when compared between groups was 6.8± 3.847 in group I (non significant) and 8.85 ±5.353 group II extremely significant and 6.75±3.640 (extremely significant) (Table:3 and Graph:3)



Graph 2: Comparison Of Anxiety Levels Among Study Groups

Table 3 Comparison Of Depression Levels Among Study Groups

GROUPS	n	MEAN	SD	P VALUE	SIGNIFICANCE
I	20	6.8	3.847±	0.17	Not Significant
II	20	8.85	5.353±	0.96	Not Significant
III	20	6.75	3.640±	0.15	Not significant

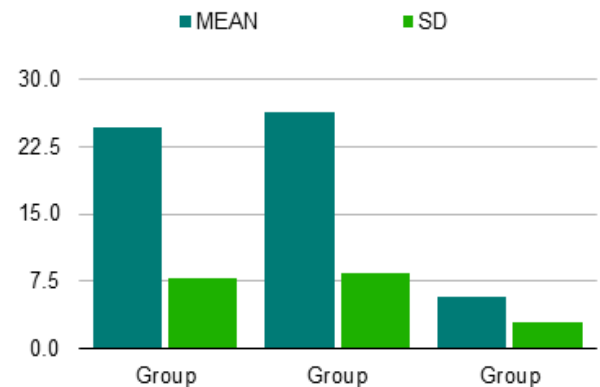


Graph 3 Comparison Of Depression Levels Among Study Groups

We calculated and compared SCL according to anxiety and between three groups and it was observed mild anxiety was seen in 31 patients, moderate in 14 patients and severe in 15 patients. Mean and SD was calculated which was 9.09±5.343, 25±4.867 and 33.46±2.695 which was statistically extremely significant with p=0.0001 (Table:4 and Graph:4)

Table 4: Comparison Of Serum Cortisol With Anxiety

Anxiety levels	n=60	MEAN	SD	P VALUE	SIGNIFICANCE
Normal	0	-	-	-	-
Mild	31	9.09	5.343±	0.0001	Extremely Significant
Moderate	14	25	4.867±	0.0001	Ext. significant
Severe	15	33.46	2.695±	0.0001	Ext. significant

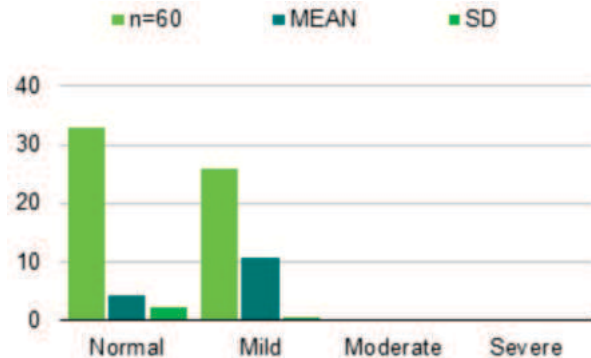


Graph 4: Comparison Of Serum Cortisol With Anxiety

We also calculated and compared SCL according to depression levels between three groups and it was observed that normal depression levels was seen in 33 patients and mild in 26 patients. Moderate and severe depression levels were not seen among any patients. Mean and SD between normal and mild levels was 4.19±2.097 and 10.73±0.050 with p value of 0.0001 was found to be statistically extremely significant (Table:5 and Graph:5)

Table 5: Comparison Of SCL According To Depression Levels

Depression levels	n=60	MEAN	SD	P VALUE	SIGNIFICANCE
Normal	33	4.19	2.097±	0.0001	Extremely significant
Mild	26	10.73	0.050±	0.0001	Extremely Significant
Moderate	0	-	-	-	-
Severe	0	-	-	-	-



Graph 5: Comparison of SCL according to depression levels

We also made an attempt to study the distribution of SCL (Table:6), Anxiety (Table:7) and Depression (Table:8) according to gender but not quite significant results were obtained.

Table 6: Distribution Of SCL Levels According To Gender

Groups	N=60	Gender	MEAN	SD	P VALUE	SIGNIFICANCE
I	12	Male	8.63	0.627±	0.6	Not significant
		Female	8.75	0.573±		
II	12	Male	7.67	2.780±	0.6	Not Significant
		Female	8.22	1.870±		
III	10	Male	5.558	0.676±	0.3	Not significant
		Female	5.99	1.054±		

Table 7: Distribution Of Anxiety Levels According To Gender

Groups	N=60	Gender	MEAN	SD	P VALUE	Significance
I	12	Male	24.75	8.465	0.9	Not significant
		Female	24.62	7.595		
II	12	Male	23.75	8.247	0.9	Not Significant
		Female	30.12	7.605		
III	10	Male	5.3	2.869	0.5	Not significant
		Female	6.1	2.960		

DISCUSSION

Cortisol is commonly recognised as the body's stress hormone, it also exerts diverse effects on various bodily functions. It serves as the primary glucocorticoid originating from the zona fasciculata of the adrenal cortex. The hypothalamus-pituitary-adrenal axis governs the production and release of cortisol. Deregulations of this axis can result in disorders characterised by excess cortisol, such as Cushing syndrome, or deficiencies like Addison disease^[6]. Cortisol plays a crucial role as a catabolic hormone and a central figure in the body's response to stress. During stressful situations, the activation of the HPA axis triggers the release of cortisol. Stress serves as the primary cause for the onset of numerous diseases^[1]. In the present study, a majority of Group I (Leukoplakia) had mild and moderate anxiety, which is in accordance with the study conducted by Kanodia et al^[10].

The present study recorded mild anxiety levels and higher mean anxiety scores in patients with leukoplakia compared to controls, while patients with OSMF had the highest mean anxiety scores among the three groups. Our study reported very few patients with severe and very severe depression, consistent with previous reports like of Kanodia et al and Manshi et al^[1,9].

Manshi et al. recorded higher mean anxiety scores in patients with leukoplakia when compared with controls same as our study, while patients with highest mean score was of OSMF they also recorded very few severe depression same as our study^[1]. Sonal et al in their study concluded the mean stress, anxiety and depression of OLP and SCC showed highly significant difference when compared to OSMF and leukoplakia^[4].

Our study found that Group II had higher mean depression scores than

the control group. Notably, Group I, consisting of patients with leukoplakia, exhibited the highest intergroup mean depression scores. This observation of elevated depression levels among patients with OSMF is unique, as few studies have shown such data^[9,10].

The study identified a highly statistically significant and strong positive correlation between anxiety, depression, and serum cortisol levels in patients with Oral Submucous Fibrosis (OSMF) and leukoplakia. This relationship, where increased depression correlates with elevated serum cortisol levels, has been previously documented. The heightened levels of depression and anxiety may be multifactorial, potentially linked to OSMF symptoms such as restricted mouth opening, difficulty eating or chewing, and speech problems. Confirming these factors would require more specific and detailed psychiatric evaluations^[10].

Additionally, the stimulatory effect of depression on the hypothalamus-pituitary-adrenal (HPA) axis may increase corticotropin-releasing hormone production, subsequently raising serum cortisol levels. Disclosure of information about the presence of a potentially malignant disorder (PMD) could itself result in anxiety and depression, warranting further investigation^[11].

Previous reports have indicated increased psychiatric morbidity in patients with advanced stages of disease, with a majority of OSMF patients experiencing moderate levels of depression. This finding aligns with the present study, which also found a strong association between psychiatric morbidity and advanced stages of OSMF and leukoplakia^[10].

Current lifestyle patterns often include addictive habits involving harmful substances such as smoking, gutkha, and tobacco use. The frequency of these habits may rise alongside increasing stress levels, which in turn heightens the prevalence of potentially malignant disorders (PMDs). Thus, it is reasonably certain that assessing psychiatric morbidity would reflect the patient's mental state, while measuring serum cortisol levels would indicate stress patterns in these diseases. Evaluating both parameters could aid in the early diagnosis and potential prevention of life-threatening diseases such as cancer. Therefore, beyond the diagnosis of these diseases, mandatory psychological counseling should be included in the treatment regimen.^[1]

CONCLUSION

The results of our investigation showed a high correlation between elevated blood cortisol levels and psychological morbidity, such as depression and anxiety, in patients with advanced stages of OSMF and leukoplakia. Such trials on patients with leukoplakia, a common PMD in India, have not yet been conducted. Larger sample numbers for future research would be beneficial in determining the association between individuals with different PMDs and other neuroendocrine abnormalities.

Conflict Of Interest: Nil

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