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Association Between Anxiety, Depression, and Salivary Cortisol Levels in Patients with Recurrent Aphthous Stomatitis

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Original Investigation

Abstract

Objective: Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease of the oral mucosa that commonly affects the general population. The objective of this study was to conduct a research in assesing the relationship between psychological disorders including anxiety, depression and salivary cortisol levels in patients with RAS.

Methods: Thirty-nine patients suffering from minor RAS were enrolled in the study after obtaining an informed consent. The control group consisted of 25 age and gender matched healthy individuals. All subjects were evaluated by using both psychological tests (Hamilton's anxiety rating scale [HARS] and Hamilton's depression rating scale [HDRS]) and physiological testing instrument (salivary cortisol level).

Results: While no statistical difference was found between the patients with RAS and controls for both salivary cortisol levels and anxiety, there was statisticaly significant difference between the groups for depression.

Conclusion: There was no significant increase in salivary cortisol levels in patients with active disease when compared to the healthy subjects. But we found that depression scale values were significantly higher in patients with RAS.

Keywords: Aphthous stomatitis, saliva, cortisol, anxiety, depression

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Introduction

Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease of oral mucosa in clinical practice. These ulcers are characterized by a rounded shallow painful ulcer with a yellowish gray pseudomembranous center and a well-defined erythematous rim (1). RAS can be examined in three types which are minor, major and herpetiform ulcers. Clinically, minor ulcers are the most common form of RAS with a tendency of lower size (less than 1 cm) and rapid healing process when compared to major type (Sutton's disease). Herpetiform ulcers are a large number of ulcers spreading to large areas along the oral mucosa. However, these ulcers are not related to the herpes simplex virus (2).

The incidence of RAS are ranged from 5% to 66% and precise pathogenetic mechanism of it is not revealed (3, 4). Although RAS usually heals within 10 to 21 days, these aphthous ulcers are often accompanied by severe pain disproportionate to the size of the lesion. For this reason there is a negative effect on the quality of life. The pain of major ulcers is more severe and its healing occurs sometimes with a scar (2).

There are many factors that influence RAS exacerbations; these include family history, nutritional deficiencies, food allergies, immune-deficiencies, smoking cessation, local trauma, genetic predisposition, systemic diseases, hormonal and emotional disorders, and similar situations (5-9). Although, the researchs evaluating the effect of psychological factors on RAS are extremely variable, the onset and recurrences of RAS may be triggered by emotional conditions such as stress and anxiety (10-16).

Acute stress is characterized by alterations in catecholamine levels. In chronic stress, alterations in cortisol level are more prominent (17). Cortisol, or stress hormone, is the most important synthesized glucocorticosteroid in the cortex of the adrenal

gland. To assess anxiety, measurement of salivary cortisol is superior to serum cortisol level. This is because when salivary cortisol level is measured, unbound cortisol is assayed. In addition, collecting salivary sample is noninvasive, does not need trained staff, is relatively nonstressful, and changes in environmental conditions such as temperature, movement, and growth of microorganisms do not change salivary cortisol level (18, 19). Additionally, the measurement of the level of cortisol in saliva has become attractive in recent years. When compared to serum cortisol level, saliva cortisol level can provide better information because of labile cortisol level in serum (18). The relationship between cortisol levels (serum and saliva) and psychological state was established in a previous study (14).

Although stress and anxiety are shown as possible factors in the development of RAS, this relationship is still unclear (3). In order to better understand the role of salivary cortisol, depression and anxiety in the development of RAS, we planned this study, and at the same time, we wanted to evaluate the relationship between anxiety and depression and salivary cortisol levels in RAS patients.

Methods

This study was approved by the Ethics Committee of the Medical Faculty of Fırat University, and was conducted in accordance with the ethical standards of the Helsinki Declaration of 2000. Data were collected between January 2015 and January 2016 after obtaining informed consent from the subjects. Thirty-nine patients with minor RAS and 25 healthy individuals (control group) were enrolled in the study. The control group was constituted similar to study group's age and sex characteristics.

Patient and control groups had no chronic disease. Detailed anamnesis (RAS family history, time of onset, predisposing factors, number of aphthous lesions in the last three months, localizations, diameters, recovery time of lesions) and full dermatological examination were performed. Pathergy test, ophthalmologic examination, whole blood count, routine biochemical tests, serum iron, folic acid, ferritin and vitamin B12 levels were examined. Patients with normal laboratory findings were included in this study. Patients with systemic disease, endocrine and metabolic diseases, blood deficiencies, steroid and other hormonal drug users, pregnant patients and Behçet's patients were excluded from the study. The diagnosis of the minor RAS was made with clinical examination and anamnesis.

Physiological evaluation

Saliva samples of the control group and study groups at the active phase of oral ulcers were obtained between 09:00 am and 09:15 am and 5 mL was collected into sterile glass tubes via passive flow without any saliva stimulus prior to the meal. All participants were allowed to wash their mouths appropriately before taking samples. After saliva samples were taken with a sterile foam-tipped applicator, these samples were centrifuged at 1000 G and stored at -20 °C. Salivary cortisol levels were measured by electrochemoluminescence method (Roche Cobas 8000/e602, Roche Diagnostic, Germany). The measurement ranges are 1.5-1750 nmol/L or 0.054-63.4 μg/dL according to the manufacturer's protocol.

Psychological evaluation (Anxiety and depression evaluation)

After the sample of saliva collection, the patients were exposed to psychological evaluation. The Hamilton anxiety rating scale (HARS) is used to describe of anxiety levels including overall anxiety, psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety) (20). This scale encompasses 14 questions, half of them are related to the psychic anxiety and the other half to the somatic anxiety. The individuals are scored from 0 to 4 on each of the 14 items. The total anxiety score ranges from 0 to 56, where <17 indicates mild severity, 18-24 mild to moderate severity and 25-30 moderate to severe. Meantime depression levels were measured by using Hamilton depression rating scale (HDRS) (21). The HDRS is designed to rate the severity of depression in patients. Although HDRS contains 21 areas, it calculates the patient's score on the first 17 answers. This first - 17 questions with a five point on each items (ranging from 0 to 2, from 0 to 3 or from 0 to 4). The total depression score ranges from 0 to 51, where <7 indicates normal, 8-13 indicates mild depression, 14-18 moderate depression, 19-22 severe depression, ≥23 very severe depression.

Statistical Analysis

Independent t-test was used to define quantitative differences between groups; and p value of ≤0.05 was considered as statistically significant. All statistical analyses were performed using the version 21.0 of the SPSS (IBM Corp., Armonk, NY).

Results

A total of 64 subjects including 39 patients and 25 as members of the control group were evaluated for age, gender, and demographic data, grade of anxiety and depression and saliva cortisol levels. Demographic data of the patients were shown in table 1. Mean saliva cortisol levels in RAS patients were 0.15377 μg/dL and 0.111804 μg/dL in the control group, and there was no significant difference between groups. The mean score of HARS was 13.72 in RAS patients and 9.79 in the control group, and no statistically significant difference was found between the two groups ($p>0.05$). The mean score of HDRS was 12.76 in RAS patients and 3.95 in the control group. The score of HDRS in RAS patients was found to be significantly higher than the control group ($p<0.05$). The patients was diagnosed with depression by a psychiatrist and antidepressant therapy was started. All statistical data regarding HDRS, HARS and saliva cortisol levels were shown in table 2.

Discussion

Oral diseases have negative influence on nutrition, speech, physical appearance and social relations. RAS affects the quality of life of the patient especially as a consequence of long episodes of disturbing pain (15). Complex factors were reported about the etio-

Table 1. Patients' demographics

	Study group (n=39)	Control group (n=25)
Females	24	11
Males	15	14
Mean age	37.25	30.7

Table 2. All statistical data regarding HARS, HDRS and salivary cortisol levels

Group	Patients with RAS	Controls	Patients with RAS	Controls	Patients with RAS	Controls
Variable	Anxiety (HARS)	Anxiety (HARS)	Depression (HDRS)	Depression (HDRS)	Salivary Cortisol Level (µg/dL)	Salivary Cortisol Level (µg/dL)
Mean	13.72	9.791667	12.76	3.958333	0.15377	0.11804
p	0.686		0.001		0.127	

p<0.05 was considered as significant
HDRS: Hamilton Depression Rating Scala; HARS: Hamilton Anxiety Rating Scala; RAS: Recurren Aphtous Stomatitis; p<0.05 was considered as significant

pathogenesis of RAS (22). Stress and many factors may play a role in the development of new lesions in RAS (4, 14, 23). However, there is little objective evidence of this relationship in many studies (24-25). The stress mechanism that causes RAS attacks is not fully understood. It was stated that an increase in salivary cortisol levels may lead to the onset of lesions (3, 14).

Salivary cortisol was used in a variety of studies to demonstrate high anxiety and stress state with safe analytical tools (26, 27). Cortisol production in the adrenal glands is regulated by ACTH secreted from the hypophyseal gland. ACTH secretion is controlled by the effect of corticotropin releasing hormon secreted by the hypothalamus in stress conditions (16, 26-28). In the case of anxiety and depression, a proportional enhancement of cortisol level in saliva was described, and also changing of plasma cortisol level (26, 28). Nadendla et al. (29) detected statistically significant increase in anxiety levels and salivary cortisol levels when compared with control groups in the inactive phases of RAS patients. The activation of the parasympathetic and sympathetic sections of the nervous system due to exposed stress leads release of hormones through hypothalamic-pituitary-adrenal (HPA) axis, and this event takes an important role in the regulation of the immunological mechanisms (15). Psychological stress increases immunoglobulin activity by increasing the number of leukocytes in the inflammation area; this is frequently observed in the pathogenesis of RAS (9, 30). Most researchers evaluated the role of stress, anxiety and depression in patients with oral diseases. When RAS patients were compared with control groups, significant levels of high stress, anxiety and depression were detected (28, 31). In this study, we found high levels of depression at a statistically significant level in RAS patients compared to the control group.

Pathophysiologic outcomes of the stress are variable in patients. Similarly, the same patient may show different responses to the same type of emotional stress (5). Even if stress-increasing factor was stated in RAS, the evidence about this relationship was not sufficient in literature (12). Albanidou-Farmaki et al. (3) studied possible relationship between RAS, salivary cortisol and anxiety. They selected 38 patients with RAS and 38 healthy control subjects and used chemoluminescent immunoassay to evaluate cortisol levels. Higher results with statistical significance were detected in the analysis of serum and salivary cortisol levels in RAS patients. Furthermore, anxiety levels in RAS patients were found to be higher than healthy individuals (3). In a study by McCartan et al. (14), cortisol levels were measured by radioimmunoassay between two different groups of patients with/without RAS, and the possible relationships were declared among anxiety and saliva cortisol levels. Though our whole results do not show a considerable rise of saliva cortisol, we found that patients with the higher saliva cortisol concentrations sorrowed more serious clinical forms of the disease.

Conclusion

As a result of this study, we can point out that we could not observe the existence of meaningfully higher saliva cortisol levels among the patients with RAS in our region during periods of active disease than in healthy individuals. Owing to the differences observed between our results and those obtained by other authors, we believe that further studies are needed in other populations with larger sample sizes. RAS-related studies were difficult to conduct because of higher heterogeneity of patients, furthermore, it was difficult to say the emotional stress causes RAS or vice versa. Thus, we will be able to identify the real role of saliva cortisol level and the real significance of stress and anxiety as launchers in the pathogenesis of the RAS.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Fırat University School of Medicine (19/05).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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