

Assessment of the Relationship Between Stress and Oral Lichen Planus: A Review of Literature

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Abstract

Background and Aim: Oral lichen planus (OLP) is a chronic inflammatory lesion. Psychological stress occurs when someone senses that environmental demands exceed his/her adaptive capability. Stress, anxiety, and depression have frequently been mentioned as possible factors related to the development of OLP, although this association remains controversial. In most studies, a positive correlation was found between psychological stress and OLP, although some found no significant association. In this review, we assess the possible role of psychological stress in the etiopathogenesis of OLP.

Materials and Methods: The methodological approach of this study was to search major databases from 1985-2014, using "oral lichen planus", "stress", "anxiety", "depression" and "psychological disorder" as search terms.

Results: A total of 45 scientific papers and abstracts in English were reviewed, and 10 articles met the necessary requirements. Stress evaluation methods of these articles were questionnaire, genetic polymorphisms at DNA level, measurement of body substances like hormones, and effect of drug therapy of psychiatric disorders on OLP patients. In order to include a study, OLP in patients must have been proven by clinical and histopathological criteria. Exclusion criteria were not explicit stating the OLP diagnosis, an inadequate number of the test subject in experimental and control groups, discrepancy (inconsistency) in sex and age between the case and control groups, and unreliable method of stress measurements.

Conclusion: Higher levels of stress in patients with OLP were confirmed. Reducing psychological stress and well-being of patients is an important factor that should be considered in the treatment of OLP.

Key Words: Stress, Psychological, Lichen planus, Oral, Anxiety

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Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease. The prevalence of OLP differs from 0.9 to 2.2 percent in the general population [1,2]. Lichen planus is characterized as an adult disease and females are more suffered

than males [3,4]. Nowadays certain clinical and histopathologic criteria of OLP are well-known [5,6]. Oral lichen planus is an oral lesion with an inexplicable etiology [7]. Its etiopathology is still uncertain [8] however, there is considerable data to suggest that immunological mechanisms are

fundamental in the initiation and perpetuation of lichen planus [9]. Since the description of lichen planus by Wilson, the balance is tilting toward psychosomatic stressors being discussed as one of the causative factors. The association of psychosomatic factors and dermatological disorders are well recognized, their importance in OLP is not clear yet [1]. Stress, anxiety, and depression have frequently been mentioned as possible factors related to the development of OLP, although this association remains controversial [10]. In the most studies, a positive correlation was found between psychological stress and OLP [1,11,12,13,14], although some studies found no significant association [15,16]. Psychological stress happens when an individual feel that environmental demands load exceed his capacity [17]. Anxiety is an emotion explained and recognized by feelings of anxious thoughts, nervousness and physical changes like increased blood pressure [18]. Depression is a common mental illness which can be characterized by sadness, lack of interest and tedium, feelings of guilt or low self-esteem, sleep deprivation, loss of appetite, feelings of tiredness, and poor concentration [19]. Therefore, regarding these controversies about the relationship between stress and OLP more research on this subject are needed. In this review, we assess only the possible role of psychological stress in the etiopathogenesis of OLP.

Materials and Methods

We have searched the following databases from 1985 to 2014: the Cochrane Controlled Trials Register, Pubmed, Medline, Ovid, Google Scholar and Embase. The search terms which obtained from Medical Subject Heading (MeSH) were "oral lichen planus", "stress", "anxiety", "depression" and "psychological disorder". A total of 45 English language full texts and abstracts were reviewed, and 10 relevant articles identified. The remaining articles were rejected for one or more of the following reasons: 1) the criteria for diagnosing OLP were not stated; 2) only the relationship between OLP and anxiety or depression or psychological disorder was evaluated and the role of stress was not mentioned; 3) the number of participants in the case and control groups was not

sufficient; 4) the sex and age of participants in the case and control groups were not matched; 5) stress level measurement methods were not reliable (Table 1).

The remaining articles satisfied the following criteria:

- OLP in patients was proven by clinical and histopathological assessments.
- Psychological stress was diagnosed and established by questionnaires or measurement of body substances like hormones (Table 2).

Results and Discussion

Table Stressful events influence the pathogenesis of physical disease by direct effects on biological processes or behavioral patterns that influence on disease risk [17]. Psychological stress also activates the following two endocrine response systems:

1- Hypothalamic-pituitary-adrenal (HPA) axis; stressful and traumatic events increase stress hormones [20] and cortisol controls a wide-range of physiological processes, including anti inflammatory responses [17,21,22].

2-Sympathetic-adrenal-medullary (SAM) system; Catecholamines, neuropeptides, and neurotrophins which are released in response to SAM activation, alter immune response profoundly [20]. Prolonged or repeated activation of the HPA and SAM systems can interfere with their control of other physiological systems, resulting in increased risk of physical and psychiatric disorders [17]. Even mild transient stress can induce immune dysregulation and a decrease in the function of lymphocytes [15]. The influence of stress on the immune system and inflammatory process have the ability to influence depression, infection, autoimmune and coronary artery disease, and ultimately cancers via viral mediation [17,21].

Patients with a psychological condition are usually placed in one of two groups, "stress responders" for whom there is a close relationship between stress and exacerbation of the disease, and "non-stress responders," whose mucosal disorder is independent of their emotional status [17]. Recent studies imply that psychological stress is an important factor in the causation of OLP [11, 12].

In the present review, four types of studies were found and will be discussed in the following

Table 1. List of excluded articles and the reason of their elimination

Author(s)-Year	Number of cases	Type of study	Reason (s) of exclusion
Mohamadi Hasel K, et al.,2013 (20)	60 Cases	Retrospective	The relationship between personality factors with depression, stress, and OLP was assessed, not the stress and OLP Hamilton anxiety scale was used for stress evaluation.
Ranpise SG, et al.,2011 (23)	28 Cases 32 Controls	Case control	

Table 2. Synopsis of included articles

Author(s)-Year	Number of cases	Type of study	Stress assessment	Result
Allen CM, et al.,1986 [28]	Case:48 Control:76	Case control	Questionnaire (Social re-adjustment rating scale)	No significant differences were seen among groups
Soto Araya M, et al. 2004 [12]	Case:9 Control:25	Case control	Questionnaire (Test of recent experience)	Positive relation between stress and OLP
Chaudhary S,2004 [1]	Case:41 Control:109	Double controlled study	Questionnaire (General Health Questioner version 28)	Significantly higher stress was seen in OLP patients
Ivanovski K, et al.,2005 [7]	Case:40 Control:25	Blind case-control	Questionnaire (MMP 1-202 psychology test, IR index emotional status)	Mean values for stress were significantly higher in both reticular and erosive OLP subjects compared to controls.
LundqvistEN, et al., 2006 [11]	Case:49 Control:357	Case control		Stress were more common in erosive OLP
Perdigão PF, et al., 2007 [15]	Case:44 Control:54	Case-control	measuring serotonin transporter gene polymorphism	No association found between OPL and Serotonin transporter gene polymorphism
Shah B, et al., 2009 [14]	Case:30 Control:30	Case-control	Salivary cortisol measurement & stress scale	Higher level of stress in OLP
PokupecJS, et al.,2009 [5]	Case:1	Case report	Questionnaire(projective test, anxiety tests, depression test)	Comorbidity of lichen planus with the occurrence of depression and anxiety suggest that oral diseases have a psychogenic component
Girardi C, et al.,2011 [16]	Case: Control:	Case control	Lipp's Inventory of stress DHEA and cortisol levels	There was no significant difference between stress and OLP or morning and night salivary levels of DHEA and cortisol
PourshahidiS, et al.,2011 [13]	Case:52 Control:47	Case control	Questionnaire (General Health Questioner version 12 & Perceived stress scale)	Patient with erosive OLP have significant higher stress level

sections:

- Studies in which questionnaires were used to evaluate the level of stress in patients with oral lichen planus and in the control group
- Investigating genetic polymorphisms at DNA level in patients with OLP and comparing them to the control group
- Measurement of some substances in the body which are related to stress such as hormones
- Evaluating the effect of drug therapy of psychiatric disorders on lichen planus.

Questionnaire Group

Stress initiates various autoimmune reactions, which contribute to the pathogenesis of OLP. Using the general health questionnaire (GHQ) in 2004, Chaudhary [1] found significantly higher levels of stress in OLP patients. Also in 2004, a case-controlled study was carried out to determine the relationship between OLP and psychological changes, such as stress, in the patients. The Test of Recent Experience was used to measure the stress level. The results showed a statistically significant association between psychological status and oral mucosal diseases. The results also proposed that psychological factors should be taken into consideration in the establishment of normal healthy mucosa [12]. In another case-controlled study by Pourshahidi et al, [13] the relationship between OLP and stress was evaluated using General Health Questionnaire version 12 and Perceived Stress Scale. Significantly higher levels of stress were found in both reticular and erosive forms of OLP patients compared to the control group. However, no significant difference was found between reticular OLP and erosive form. Altogether, it has been found that an important factor in causing OLP is psychological stress [13]. In a 2006 case-controlled study by Lundqvist et al, (11) psychological health of patients with genital and oral erosive lichen planus was evaluated by PSQ Questionnaire. It has been revealed that 87% of patients had life altering severe symptoms, 70% of patients have been diagnosed with moderate levels of stress while only 8% of the control group have been detected with fairly increased stress. High levels of stress were reported in 13% of patients and 3% of the control group, and no differences was detected between women and men within the groups. Erosive oral lichen planus is a

suffering disease that may even be life threatening. Most patients have severe symptoms such as irritation, burning, and pain that affects their well-being. Also, it has been previously shown that worsening and increase in the severity of OLP was associated with periods of psychological stress and in certain patients, the symptoms of stress may intensify their somatic symptoms [11]. Altogether there is no doubt that stress is more common in patients with multifocal erosive lichen planus that signifying impaired psychological health. Therefore the psychological aspects are greatly important. The origin of mental conditions has to be further studied in order to ascertain whether the stressed state is an outcome of the pain associated with erosive OLP, or the cause is interactive processes between symptoms of OLP lesions and a vulnerable personality [11]. Ivanovski et al, [7] in 2005 have shown that mean values for stress were significantly higher for both erosive and reticular OLP subjects compared to control group using MMPI-202 Test. They also concluded that prolonged psychological stress may lead to initiation and clinical manifestation of OLP [7]. Similar results were reported by Pokupec et al, [5] in their case-control study.

The synchronicity of the emotional stress and any type of OLP indicates that this oral disorder has a psychogenic component.

Genetic Polymorphisms Group

In several articles, the relationship between stress and genetic factors has been evaluated however, we found only one study in which the association of serotonin transporter gene polymorphism with OLP has been assessed [15]. The serotonin transporter gene polymorphism (5-HTTLPR) regulates the duration and magnitude of serotonergic neurotransmission and can influence stress in patients with OLP. Perdigao et al. [15] compared the 5-HTTLPR in OLP patients to the control group. They detected no statistical differences between the OLP and control group, nonetheless, the low number of patients with the erosive type of OLP compared to reticular type might result in a false negative association. However, the stress might be the consequence and outcome of the disease, not the cause, the conclusions of the article may be admissible and justifiable [15].

Due to limited study in this area, further research is needed for accurate conclusions.

Measurement of Like Hormones Group

Clinical studies suggest that increased levels of cortisol may induce clinical depression. Salivary cortisol as a stress hormone was evaluated by Shah et al, [14] in 2009. A self-reported scale, called DASS, was used in this study. Increased levels of stress were found among all the patients compared to controls. Stress was increased in all forms of OLP and there were no statistical differences between erosive and non-erosive groups. Increased salivary cortisol levels were observed among 56.6% of OLP patients. In the reticular, erosive, and combined patterns of OLP, the level of salivary cortisol was increased compared to linear and annular patterns. A positive correlation between stress and salivary cortisol levels was found using Pearson's correlating coefficient ($P < 0.001$). Secretion of cortisol in saliva is a reliable indicator of levels in the serum and salivary sampling is a non-invasive and easy procedure. In their study, erosive and non-erosive OLP patients had similar levels of stress [14]. In a study by Girardi et al, [16] the level of dehydroepiandrosterone (DHEA) and the score of stress in patients with OLP were determined and no significant difference between OLP patients and controls was detected. There was also no difference between levels of salivary DHEA and cortisol in the morning and at the night [16].

Ranpise and John [23] have shown that stress is an inducer of OLP and 17-ketosteroid in urine. In their study, saliva was used as an indicator of underlying psychological stress. 17-ketosteroid is secreted by the cortex of the adrenal gland in blood in two forms: conjugated (depends on protein bound level) and unconjugated (related to adrenal cortex directly). A urinary steroid which is the metabolites of the primary hormones also is considered as conjugated, so 24-hour sampling for estimation is needed to include all of the metabolites. Because saliva contains free unconjugated steroids, it is a true reflection of adrenal cortex function. 17-ketosteroid in the saliva was found to be a true monitor of glucocorticoids, which varies consistently in plasma. OLP patients had different levels of 17-ketosteroid in both saliva and urine. They have

concluded that this method could be utilized as an indicator of psychological stress and would be helpful in treatment planning [23].

The results of these studies seem contradictory to each other probably due to differences in their approaches, for example, time of sampling, type of hormone that was assessed, and method of measurement. Therefore, to achieve reliable results, more case-control studies with larger number of participants are needed.

Drug Therapy Group

Delavarian et al. [4] have found that drug therapy of psychiatric disorders in stressed patients along with traditional treatment of OLP could reduce the size of lesions, thus reducing the amount of corticosteroid and related side effects [4]. In another study by Delavarian et al, [4] in 2010, the effect of treatment of the psychiatric disorder in OLP patients was evaluated. The decrease in lesion size was significantly higher in the case group and although the pain severity and alteration in the form of the lesion (erosive and atrophic to keratotic) were decreased, they were not statistically significant. However, in this study, the authors had focused on anxiety and depression and not directly on stress [4].

In summary, it is reasonable to treat psychologic disorder along with routine treatment of OLP. Stress may affect the immune system either directly or indirectly through the nervous and endocrine systems. Increasingly, interdisciplinary psychoneuroimmunological research shows clinically relevant association between psychological stressors and the onset and progression of chronic disorders.

Dysregulations of interaction between the nervous system, the immune system, and the endocrine system have been described to be implicated in several endocrinological autoimmune diseases.

Evaluation of the Effect of Stress on Immune System

The effect of psychological and physical stress on the immune function has been demonstrated in many human and animal studies. It has been shown that in up to 80% of patients with the autoimmune disease had an onset emotional stress before their illness has been reported [24]. Some investigators have documented that stress is a participating factor in

the initiation and exacerbation of autoimmune disease [24].

Many studies have suggested that the imbalance between Th1/Th2 has a critical role in the pathogenesis of several autoimmune disorders such as Behcet disease (Th1 dominant), Sjogren syndrome (Th2) and psoriasis (Th1) [25].

T lymphocytes promote their function through cytokine release. Generally, Th1 cytokines include IL-2, IL-12, IFN- γ , and TNF- α , and Th2 cytokines consist of IL-4, IL-5, IL-6, IL-10, and IL-13 [26].

It has been postulated that repeated episodes of acute or chronic stress can induce an acute phase response that results in a chronic inflammatory process such as autoimmune disorder [24]. One of the most common cytokines in this process is IL-6 which is a part of the innate immune system and produced by the liver, the endothelium, monocytes, macrophages, T&B cells, and fat cell depots. IL-6 has a key role in acute phase response, differentiation and stimulate on of B cells, and growth and differentiation of T cells, that lead to chronic phase and autoimmune disease like OLP [24,26]. Some studies have indicated that levels of IL-6 are increased in OLP patients while others believe that levels of IL-6 are decreased [17]. It has been hypothesized that the decreased levels of IL-6 in OLP patients may suppress an immune response that eventually leads to induction of the inflammatory process in OLP [17].

Evaluation of the Effect of Stress on Hormonal System

To maintain homeostasis, activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system during stress leads to an increased secretion of glucocorticoids and catecholamines. Several studies on the circadian rhythm have identified a negative correlation between numbers of circulating T-cells and amounts of blood cortisol [24]. Stress hormones, acting on antigen-presenting immune cells, may affect the differentiation of helper T-cells away from a Th1 and towards a Th2. It means suppression of cellular immunity and activation of humoral immunity. Moreover, most investigations have suggested the possible role of humoral immunity in the pathogenesis of OLP [24]. For example, auto-antibody against desmoglein 1&3 in OLP has been found. In most of the studies that we

have reviewed, the concentration of cortisol was shown to have an increased in OLP patients [24].

It might be assumed that this elevation is due to a compensatory mechanism of the adrenal glands to counter disease. Also, in Cushing's patients, removal of adrenal glands leads to deterioration of autoimmune disease [27].

During the stress, neuroendocrine hormones cause a change or amplification of cytokine production result in immune dysregulation, atopic autoimmune diseases, and/or diminished host defense. There are different types of transmitter substances of the neuroendocrine-immune system including epinephrine, norepinephrine, acetylcholine, substance P, vasoactive intestinal peptide, glucagon, insulin, cytokines, growth factors, and numerous other mediators. Catecholamines induce an increase in CD8+ and NK cell in peripheral blood [27]. Band-like infiltration of lymphocytes in lamina propria and keratinocyte apoptosis are two major criteria for the diagnosis of OLP. Existing data has confirmed a preponderance of CD8+ T-cells in the intraepithelial layer. These lymphocytes are involved in antigen presentation, lymphocyte activation, proliferation, and migration as well as keratinocyte apoptosis [28].

In order to assess the true relationship between stress and OLP, a longitudinal study must be designed because OLP is an autoimmune disease and has exacerbation and remission phases with different levels of cytokines and pathogenesis. Additionally, we suggest the use of both questionnaire and laboratory studies in both phases of the disease with a sufficient number of participant in case and control groups.

Conclusion

Oral lichen planus is a psychosomatic disease and literature confirms the presence of higher levels of stress in patients with OLP. Underlying psychological stress plays an important role in causing the OLP. Some articles have suggested that stress may not initiate the OLP development, rather than OLP can lead to psychological stress by altering patient self-image and influencing their public interactions. Therefore, psychological well-being is an important factor that should be considered in the treatment of these patients.

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