

# THE RELATIONSHIP BETWEEN THE ORAL LICHEN PLANUS AND ENDOCRINE HORMONES: A REVIEW OF LITERATURE

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## Abstract

Today, the Oral Lichen Planus (OLP) is known as an autoimmune mucocutaneous disease with a chronic inflammatory course that involves oral mucosa. Etiology and pathogenesis of this disease has not been properly understood. Among the possible causes are systemic drugs, dental materials, chronic liver diseases, hepatitis, genetics, tobacco chewing, psychological stress and some hormones. An extensive review was conducted on scientific resources to provide a comprehensive overview of the relationship between OLP and different hormones. This was done by searching PubMed, Ovid, and Google Scholar in December 2017 and January 2018 by reviewing 29 English-language articles published between 1990 and 2017, in which the keyword searches selected in the Mesh included Lichen Planus, Steroid hormones, thyroid hormones, and diabetes mellitus. According to the literature review, oral lichen planus is associated with thyroid hormones, corticosteroids and diabetes mellitus, but it is more evident in corticosteroids. Thyroid hormones have also been associated with hypothyroidism, but more studies are needed to prove it. Generally speaking, it seems that the study of hormonal profiles in patients with oral lichen planus lesions is significantly important. Therefore, the study of endocrine status in patients with lichen planus is recommended.

**Key words:** *Oral Lichen Planus, Endocrine Hormones.*

## Introduction

Today, the Oral Lichen Planus (OLP) is known as an autoimmune mucocutaneous disease with a chronic inflammatory course that involves oral mucosa with a relatively high prevalence; i.e. 0.5-2%. It affects mostly patients aged 30-60 years and is more prevalent in females than in males.<sup>1</sup> Six clinical types of OLP have been identified and described; but erosive and atrophic types have the most common malignant changes. In various articles, OLP is considered a pre-malignant or pre-cancerous lesion.<sup>2</sup> Some studies have reported that oral squamous cell carcinoma (OSCC) can be developed at the site of the OLP,<sup>3</sup> and this is the most important clinical problem in relation to the OLP.<sup>4</sup>

Etiology and pathogenesis of this disease has not been properly understood. Among the possible causes are systemic drugs, dental materials, chronic liver diseases, hepatitis, genetics, tobacco chewing, psychological stress and some hormones. The immune system plays an important role in the development of this disease. The role of psychological stress in this disease is also very important; and patients have repeatedly reported the incidence or exacerbation of lesions in the periods of psychological stress.<sup>5</sup> Psychological stress affects the immune system. The proposed mechanisms cause dysregulation of the immune system, changes in the balance between Th1/Th2 cytokines and increased response of Th2 to the development of autoimmune diseases.<sup>6</sup> During the periods of psychological stress, the hypothalamic-pituitary-adrenal axis (HPA axis) is activated, leading to the release of cortisol from hypothalamus.

Imbalanced secretion of normal hormones as well as endocrine and neuroendocrine hormones such as cortisol, peripheral estrogens, glucocorticoids and catechol amines, along with other factors, reduce immunity to antibodies and cause some autoimmune diseases such as lupus

erythematosus, rheumatoid arthritis, diabetes, thyroid diseases, Lichen Planus, etc.<sup>7</sup>

Most autoimmune diseases occur simultaneously with estrogen changes such as those occurred during menopause or pregnancy.<sup>8</sup> Estrogen changes are effective in the development of autoimmune diseases. The incidence of most autoimmune diseases, such as lupus and rheumatoid arthritis in women, clearly highlights the role of sex hormones in their incidence. As a stimulant to the immune system, estrogen and prolactin hormones in women accelerate the onset of lupus and early mortality in some types of this disease.<sup>9</sup>

A relationship has been found between the hormonal (Th2) and cellular (Th1) immune responses about cortisol immune regulator function. Cortisol has been shown to reduce the secretion of adrenal and cortisol androgens in patients with rheumatoid arthritis.<sup>7</sup>

Through causing the secretion of neuroendocrine hormones, physiological and physical stresses may lead to dysregulation, alteration, or augmentation of cytokine products and consequently develop the immune system diseases. Different components of the immune-endocrine-neuronal network transmitter include norepinephrine, acetylcholine, substance P, VIP vasoactive peptide, glucagon, insulin, cytokines, growth factors, and other mediators.<sup>10,11</sup>

The coincidence of many diseases, such as diabetes, chronic hepatitis C, lupus erythematosus, Hashimoto's thyroiditis and other autoimmune diseases, as well as diseases associated with some hormones have been reported in patients with OLP. In the last decade, a relationship between OLP, hypothyroidism and Hashimoto's thyroiditis has been reported in some studies.<sup>9</sup> It seems that the autoimmune base is common in the pathogenesis of OLP and Hashimoto's thyroiditis.<sup>12</sup>

The prevalence of diabetes mellitus and abnormal glucose tolerance test in people with Lichen Planus is 14-85%, which is higher than that of healthy population.<sup>13</sup> The autoimmune background of the two diseases can provide a similar pathogenesis for two diseases. However, an increased incidence of oral Lichen Planus has been reported in both insulin-dependent and insulin-independent diabetes.<sup>14</sup>

Vitamin D is a pro-steroid hormone with multiple systemic effects, including immune system regulation. The effect of serum levels of this vitamin has been reported on the progression of some diseases, including psoriasis and oral cancer. Among the vitamins, the role of vitamin D in the treatment of autoimmune diseases has been very much considered. Epidemiologic evidence also shows that there is a significant relationship between vitamin D deficiency and autoimmune diseases.<sup>9</sup>

The purpose of this study was to provide a new and comprehensive overview of the relationship between OLP and endocrine hormones.

## DIABETES MATERIALS AND METHODS

An extensive review was conducted on scientific resources to provide a comprehensive overview of the relationship between OLP and different hormones. This was done by searching PubMed, Ovid, and Google Scholar in December 2017 and January 2018 by reviewing 29 English-language articles published between 1990 and 2017, in which the keyword searches selected in the Mesh included Lichen Planus, Steroid hormones, thyroid hormones, and diabetes mellitus. In the present study, the articles were divided into [four] groups of steroid, thyroid diabetic hormones and vitamin D3, which are categorized in Table 1.

## Discussion

### *Lichen Planus and Steroid Hormones*

In the face of stress, the cortisol level increases, resulting in the disequilibrium between Th1 and Th2 levels, and therefore, predisposing a person to autoimmune diseases. Stress causes physiological reactions in the brain followed by the activation of physiological systems such as the immune system, endocrine and neurology. The activation of neuro-hormones by physiological stress occurs largely through the hypothalamic-pituitary-adrenal axis (HPA axis), which leads to the upregulation of stress hormones such as CRH, ACTH and glucocorticoids.<sup>15</sup>

These stress-related hormones increase mediators such as neuropathic anurotropin, leading to the deep changes in the immune responses.<sup>16</sup>

Since OLP is also an autoimmune disease, and its incidence or exacerbation has been reported in the periods of stress, it is not unreasonable to include cortisol in the pathogens of the disease.<sup>6</sup> Although different studies have different results, and no relationship [between the hormones levels and development of OLP has been reported,<sup>7</sup> Pippi et al. reported a decrease in the salivary cortisol secretion in the

patients with OLP. This decrease is noticeable in the morning due to the inability to produce cortisol in the event of stress in these patients.<sup>17</sup> In a study, by collecting the saliva cortisol in the morning - when the amount of secretion is maximal - Koray et al. found that there was a significant increase in the level of cortisol in the OLP group compared to the control group.<sup>18</sup> In another study conducted by Mehdipour et al (2016), the relationship between the anger expression and OLP was investigated and a positive relationship was reported between the two.<sup>19</sup>

Estrogen is another corticosteroid that is effective on all major immune cells including B cells, T cells, APCs (antigen presenting cells) and monocytes, and its receptor is seen in all lymphoid and non-lymphoid cells. It is also effective in the development of autoimmune diseases.<sup>20</sup> Estrogen increases the production of interferon gamma from T lymphocytes and increases their activity.<sup>21</sup> Estrogen activates monocytes and granulocytes, and it has been observed that during the pregnancy period, with an increase in the estrogen level, the amount of T lymphocyte production also increases. Estrogen increases the production of monocytes and granulocytes from bone marrow.<sup>22</sup> Long-term use of estrogen in animal models has shown that estrogen reduces bone marrow mass and thymus, i.e. the organs that play an important role in the removal of autoreactive cells. Therefore, estrogen causes atrophy of these organs and increases autoreactive cells in the peripheral organs.<sup>23,24</sup> It is noteworthy that the effect of estrogen on the immune system, especially the lymphocytes B, T and TNF $\alpha$ , depends on its dose, so that high estrogen doses reduce the amount of TNF- $\alpha$  production and suppress B and T lymphocytes. In fact, estrogen has an immunosuppressive activity at high doses, but at lower doses, it increases the production of TNF- $\alpha$  and activates the humoral and cellular immunity.<sup>21,25</sup> Perhaps the reason for the higher incidence of OLP in older women is the lower levels of estrogen in these individuals than in younger women.

Regarding the effects of estrogen on the control of the immune system and oral mucosa and the higher incidence of lichen planus in middle-aged women,<sup>1</sup> the role of estrogen in the pathogenesis of oral lichen planus can be considered.

But in addition to the hypothesis of the estrogen's role in oral Lichen Planus, another hypothesis can be raised regarding the cause of estrogen uptake in people with this disease.

In a study, Maurizio Cutolo et al. concluded that the inflammatory cytokines such as interleukin 1, interleukin 6 and TNF $\alpha$  activate the aromatase enzyme in the peripheral tissues. This enzyme causes the conversion of androgens to estrogen; and therefore, the increased activity of aromatase enzyme induced by inflammatory cytokines can justify the increase in the level of estrogen in this disease and autoimmune diseases; because in these diseases, the level of TNF $\alpha$ , interleukin 1 and Interleukin 6 increases significantly. The increase in the production of



inflammatory cytokines and the activation of aromatase enzymes has been more evident in the inflamed tissues. This mechanism has been shown to increase the level of serum estrogen in patients with lupus and rheumatoid arthritis, leading to the increased activity of the aromatase enzyme in the skin and mucous membranes of the patients with lupus.<sup>26</sup>

#### ***Lichen Planus and Thyroid Hormones***

The prevalence of Hashimoto's thyroiditis in OLP patients is more common than the general population. In the study of Muzio *et al.*, anti-thyroid antibodies are considered to be the initiator of autoimmune response in the mucous membranes and skin, which can lead to lichen lesions.<sup>12</sup> This issue is more likely to occur after OLP in patients with thyroid dysfunction, because asymptomatic chronic autoimmune is found in a large number of patients with thyroiditis. Screening of thyroid dysfunction is recommended especially in women over the age of 40 with OLP.<sup>27</sup> Since keratinocytes may express the TSH receptor and the thyroglobulin gene; and thyroid peroxidase antibody is more important in the pathogenesis of Hashimoto's thyroiditis, it can be assumed that the TPO antibody may have a cross reaction with a membrane protein of keratinocytes. The cytotoxic T lymphocyte antigen 4 (CTLA-4) has recently been recognized as involved in the development of susceptibility to Hashimoto's thyroiditis, and since the expression of this gene can increase the activity of T lymphocytes, the ability to develop other autoimmune diseases such as OLP increases.<sup>12</sup>

In the study of Siponen *et al.* (2010), there was no significant relationship between OLP and thyroid diseases in Filipino population.<sup>28</sup> In the study of Garcia-Pola (2015), levels of T4 and TSH were measured in OLP patients, and it was concluded that OLP and thyroid diseases, especially hypothyroidism, are comorbid conditions.<sup>29</sup>

#### ***Lichen Planus and Diabetes Mellitus***

In the studies conducted in this regard, some researchers have measured the prevalence of diabetes in people with Lichen Planus and some others studied it in diabetic patients.

Concerning the relationship between Lichen Planus and diabetes, several studies have been conducted with contradictory results. In some studies, there was no increased prevalence of diabetes in participants with Lichen Planus, and in others, there was no increase in the prevalence of this disease in the healthy participants.<sup>12</sup> For the first time, the prevalence of diabetes in patients with oral Lichen Planus was determined by Grinspan *et al.* as equal to 40%.<sup>30</sup>

In the study of Guggenheimer *et al.*, a 0.5% prevalence of Lichen Planus was found in the participants with insulin-dependent diabetes.<sup>31</sup> In the study of Atefi *et al.*, a 20% prevalence of diabetes has been reported in patients with Lichen Planus. The incidence of Impaired Fastig Glucose (IFG) was reported as 17.5%.<sup>12</sup> Meanwhile, in 1993, the

IFG was determined by Bussell as 12.8%.<sup>32</sup> Chrisrensen's study found no relationship between the two diseases.<sup>33</sup>

There are various assumptions about the relationship between these two diseases including the common etiologies of the two diseases, diabetes and Lichen Planus; and some have also suggested that the diabetes medicines are the causative agent of leukoid lesions.<sup>12,34</sup> On the other hand, in some studies, the cause of the simultaneous incidence of similar age ranges of the two diseases and the absence of any other proven relationship has been discussed.<sup>33,35</sup>

#### ***The relationship between OLP and Vitamin D3***

Although there was no consensus about the relationship between vitamin D and the immune system until about two decades ago, the studies of the recent years indicated the prominent role of this vitamin in the immune system. Vitamin D receptors are abundant in the T lymphocytes and macrophages, and most commonly in non-Thymus immune cells and mature CD8 T lymphocytes.<sup>10</sup> The possible mechanism for these repressive effects on autoimmune diseases has also proposed, so that vitamin D produces IL-4 and the transforming growth factor B1 (TGF- $\beta$ 1), which suppresses the inflammatory activity of the T-cell.<sup>11</sup> In a study entitled "The investigation of vitamin D levels in the patients with oral SCC and expression of VDR gene in pre-cancerous oral lesions", VDR gene expression was measured in 5 healthy participants, 11 participants with lichen planus and 42 participants with oral SCCs. The serum levels of vitamin D were also studied in these individuals. The results showed that VDR expression in the participants in the prognosis and development phases of oral SCC was significantly higher than normal participants. The expression of VDR was significantly reduced in patients with oral SCC. They also suffered from severe vitamin D deficiency.<sup>14</sup> In a descriptive cross-sectional study conducted by Seif, 66 patients with oral lichen planus and 30 healthy participants were studied. Serum vitamin D levels were measured using ELISA method and indicated decreased serum vitamin D level in ghdd percentage of patients with oral lichen planus.<sup>9</sup>

#### **Conclusion**

According to the literature review, oral lichen planus is associated with thyroid hormones, corticosteroids and diabetes mellitus, but it is more evident in corticosteroids. Thyroid hormones have also been associated with hypothyroidism, but more studies are needed to prove it. Regarding diabetes, from the review of the total number of articles, it seems that the level of glucose in patients is associated with the incidence of Lichen planus lesions. But the question of which disease is a prelude to the development of another diseases or that assumption that they occur simultaneously require more studies. Regarding the relationship with vitamin D deficiency, there appears to be a relationship between the decrease in its level and the development of OLP.

Generally speaking, it seems that the study of hormonal profiles in patients with oral lichen planus lesions is significantly important. Therefore, the study of endocrine status in patients with lichen planus is recommended.

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Author & year	Study design	Number of patients	Evaluated substance	Method of evaluation	Result
Girardi et al 2011	Case-control	31	Salivary of Cortisol, dehydroepiandrosterone (DEPA)	Radioimmuno assay	No relationship
Lo Muzio et al 2013	Case-control	105	anti-TPO, anti-Tg, TSH	Serum analysis	possible association
Koray et al 2003	Case-control	80	salivary cortisol	ELISA	Significant high level of cortisol
Arduino et al 2017	case-control	549	TSH, T4	Serum analysis	possible coexistence
Perez et al 1996	Case-control	99	Estrogen receptor (ER), Progesteron receptor (PR)	Immunohistochemistry	Significant increase in PR
Pippi et al 2014	Case-control	20	Cortisol	Saliva analysis	Significant reduction of cortisol
Cemil et al 2017	Case-control	32	Corticotropin-releasing hormone (CRH) receptor type 1	IHC analysis of the tissue	Significant increase in OLP
Atefi et al 2012	Discriptive	80	FBS	Blood sampling	Positive association
Ahmed et al 2012	Discriptive	86	OLP criteria	Histopathology	Positive association
Christensen et al 1977	Discriptive	123	Glucose tolerance test	Blood sampling	No association
Siponen et al 2010	Case-control	222	Any history of thyroid disease	History taking	No association
Garcia-Pola et al 2015	Case-control	215	TSH, T4	Serum analysis	Positive association
Seif et al 2018	Cross sectional	66	Vitamin D	Serum analysis	Positive association

Table 1: Articles evaluating the relationship of lichen planus and Hormones from 1990 up to now.