

Lack of Association between Estrogen and Progesterone Receptors and Oral Lichen Planus

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Abstract

Background: Lichen planus is a T-cell mediated autoimmune and chronic inflammatory disease that affects the skin and the mucous membrane. The results of numerous studies on oral mucosa have confirmed the effects of sex hormones on oral mucosa and the expression of estrogen (ER), progesterone (PR), and androgen receptors.

Lichen planus is a common disease in middle-aged women. Therefore, the present study aimed to investigate the expression of ER and PR in patients with oral lichen planus (OLP).

Method: The participants consisted of sixty-six women. The biopsy specimens of these patients were stained via immunohistochemical staining for the detection of estrogen and progesterone markers.

Results: Despite low levels of sex hormones following menopause, ER and PR levels were lower in menopausal patients with lichen planus compared to the control group. The results also showed no significant difference in the percentage and severity of ER and PR expression in healthy non-menopausal women, menopausal women with OLP, non-menopausal women with OLP, and healthy menopausal women.

Conclusion: Low ER and PR levels in oral mucosa of the OLP patients suggest a more pronounced role of receptors on the surface of immune cells than mucosal cells in the pathogenesis of OLP. Maladaptive feedback of sex hormones was involved in the case group.

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Introduction

Women have stronger immune system responses than men. Besides, women tend to have stronger innate and adaptive immune responses than men. These characteristics are under the influence of sex hormones (1). Different concentrations of

estrogen and progesterone modulate cellular and humoral immune systems. These hormones are also involved in the development of various autoimmune diseases including rheumatoid arthritis and lupus erythematosus. Most autoimmune diseases might develop due to changes in estrogen

concentrations during menopause or pregnancy (2). The mechanism of sex hormones depends on specific intracellular receptors that bind to DNA. These receptors detect and bind to the corresponding hormone in either cytoplasm or nucleus (3).

Two ER α and ER β specific receptors have been already detected for estrogen. ER α is predominantly expressed in tissues such as mammary glands and endometrium, while ER β is usually expressed in colon and prostate (4). Progesterone also has two forms of intracellular and surface receptors. Intracellular progesterone receptors (iPRs) are ligand-sensitive transcription factors of the nuclear receptor superfamily. They strongly bind to mineralocorticoid and glucocorticoid receptors. Progesterone membrane receptors (mPRs) couple to the inhibitory G proteins, which potentially mediate rapid progestin actions. Progesterone at high-physiologic and pharmacologic concentrations (> 200 nM) binds GRs, which are highly expressed in most immune cell types. Estrogen (ER) and progesterone (PR) receptors were detected in some oral tissues of animal and human specimens including gingiva, salivary glands, pulp, and sebaceous glands of the oral mucosa. The detection of these receptors in the oral cavity suggests that sex hormones directly bind to their receptors and change the physiology of oral mucosa. They play an important role in the health of oral epithelium and the development of oral diseases (1,5). Various studies have investigated the effects of these hormones on common oral diseases including epulis fissuratum, desquamation gingivitis (DG), pyogenic granuloma (PG), peripheral giant cell granulomas (PGCGs), and neoplastic tumors.

Lichen planus is an autoimmune and chronic inflammatory disease that affects the skin and oral mucosa. It affects 30-70% of the oral mucosa of patients. The prevalence of the disease is

0.5-2% (6). Reticular type is the most common clinical form of six types of OLP (7). The highest malignant transformations were reported in erythematous and plaque forms. The etiology and pathogenesis of this disease are not well known. The main factors involved in the pathogenesis of the disease are the immune system and autoimmune responses (8). The imbalance in the secretion (disruption) of endocrine and neuroendocrine hormones (e.g. cortisol, peripheral estrogens, glucocorticoids, and catecholamines) favors the rupture of immune tolerance, which is a key feature of some autoimmune diseases (e.g. lupus erythematosus, rheumatoid arthritis, diabetes, thyroid disease, and lichen planus) (3). Although various studies have examined the relationship between sex hormones and lichen planus, the definitive role of these hormones in the pathogenesis of OLP has not yet been confirmed. Gholizadeh confirmed the role of estrogen in OLP. However, the role of estrogen and progesterone receptors in the pathogenesis of this disease has not been examined yet. Given the malignant potential of lichen planus and the prevalence of OLP, the present study aimed to detect estrogen and progesterone receptors in tissue samples of patients with lichen planus.

Materials and Methods

The participants in this cross-sectional study included 33 female OLP patients who referred the Oral Disease Department of Tehran Dental School. Histologic and clinical tests were used for the diagnosis of the patients. They were divided into two menopausal and non-menopausal groups based on the modified WHO criteria.

The inclusion criteria were OLP patients diagnosed based on clinical and histopathologic tests, failure to receive any localized and systemic treatment for oral lichen planus one

month before conducting the study, the absence of oral lichenoid drug reaction and oral lichenoid contact reaction, no history of lupus, hepatitis C, hepatitis B, diabetes, thyroid diseases, and any systemic conditions causing lesions such as lichen planus, at least one year after the last pregnancy or breastfeeding, no history of sexual and hormonal disorders, and no history of intaking hormonal medications in the last three months preceding the study. The exclusion criteria were patients' unwillingness to participate in the study and contraindication for biopsy.

The control group was also matched with the case group in terms of age and sex. Thirty individuals were selected from the patients admitted to the Tehran Dental School and undergoing surgery for removal of the impacted wisdom tooth, frenectomy, and vestibulopathy. They were closely examined for inflammation in the tissues and identified cases were excluded from the study. The selected individuals were also divided into two menopausal and non-menopausal groups. The average age of non-menopausal women was 40 (28-52) and that of the menopausal women was 65 (51-78) in the case group. The average age of non-menopausal women was 33 (20-46) and that of menopausal women was 67 (50-85) in the control group.

Steps to immunohistochemical staining

Five-micron sections of tissues were prepared by microtome and incubated at 37°C and 54°C for 24 hours and 30 minutes. The prepared slides were deparaffinized with xylene rehydrated with a series of ethanol washes (70%, 96%, and 100%). The slides were then incubated with 0.5% H₂O₂ and methanol for 20 minutes to block endogenous peroxidase activity. They were washed with sterile water and subsequently heated with citrate buffer in an autoclave for 20 minutes at

120°C to retrieve the antigen. The slides were rinsed in PBS, H₂O₂, and distilled water and again in PBS. They were incubated with primary antibodies (1D5 FOR ER AND PR, FROM BIOGENEX, FREMONT, CA90).

The Novo Link Polymer RE 7150-K kit was used for secondary IgG antibodies. They were washed in TBS after each phase, and finally stained with Mayer's Hematoxylin. The antibodies were dehydrated and mounted with DPX. A breast carcinoma sample was used for positive control and the primary antibody replaced with normal saline was used for negative control.

The paraffin samples and blocks were selected in the first step. The selected samples should contain the adequate number of tissues for staining. All samples were mixed with 10% formalin buffer. Although time has no effect on the expression of proteins in well-fixed samples, the samples were selected from recently cultured tissues (two years at maximum). This consideration allowed easy access to the patient records. IHC staining was assessed qualitatively in all staining steps with regard to a positive control (breast cancer) and negative control (antibody replacement). IHC staining was interpreted based on the criteria routinely used in the examination of epithelial cells isolated from breast cancer tissues.

Blind examination was done by a pathologist using Olympus BX41 optical microscope for microscopic evaluation according to following criteria.

- 1) The percent of stained cells (stained nucleus):
Zero = no staining, 1 = 1-25%, 2 = 26-50%, 3 = 51-75%, and 4 = >75%
- 2) The severity of staining: 0 = no staining, +1 = weak staining, +2 = moderate staining, and +3 = strong staining

Results

The expression of different receptors in OLP patients and healthy individuals is presented in Table 1.

The expression of estrogen receptor severity (ERS) is higher in the menopausal women in the control group. However, estrogen receptor severity expression is higher in the non-menopausal patients with lichen planus (Table 1, Figures 1 & 2).

Table 1. Expression of different receptors in case and control groups.

		Groups							
		Control_None menopause		Control_Menopause		Patient_None menopause		Patient_Menopause	
		Count	Column N %	Count	Column N %	Count	Column N %	Count	Column N %
ERS	No staining	10	71.4%	11	68.8%	10	62.5%	12	70.6%
	Weak staining	4	28.6%	3	18.8%	3	18.8%	4	23.5%
	Moderate staining	0	0.0%	1	6.3%	3	18.8%	1	5.9%
	Strong staining	0	0.0%	1	6.3%	0	0.0%	0	0.0%
ERP	No staining	10	71.4%	11	68.8%	10	62.5%	12	70.6%
	1-25%	4	28.6%	3	18.8%	3	18.8%	3	17.6%
	26-50%	0	0.0%	1	6.3%	3	18.8%	2	11.8%
	51-75%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
	>75%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
PRS	No staining	13	92.9%	12	75.0%	13	81.3%	13	76.5%
	Weak staining	1	7.1%	4	25.0%	2	12.5%	4	23.5%
	Moderate staining	0	0.0%	0	0.0%	1	6.3%	0	0.0%
	Strong staining	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Ineffective	13	92.9%	12	75.0%	13	81.3%	13	76.5%
PRP	1-25%	1	7.1%	4	25.0%	2	12.5%	3	17.6%
	26-50%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
	51-75%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	>75%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	11.00	0	0.0%	0	0.0%	0	0.0%	1	5.9%

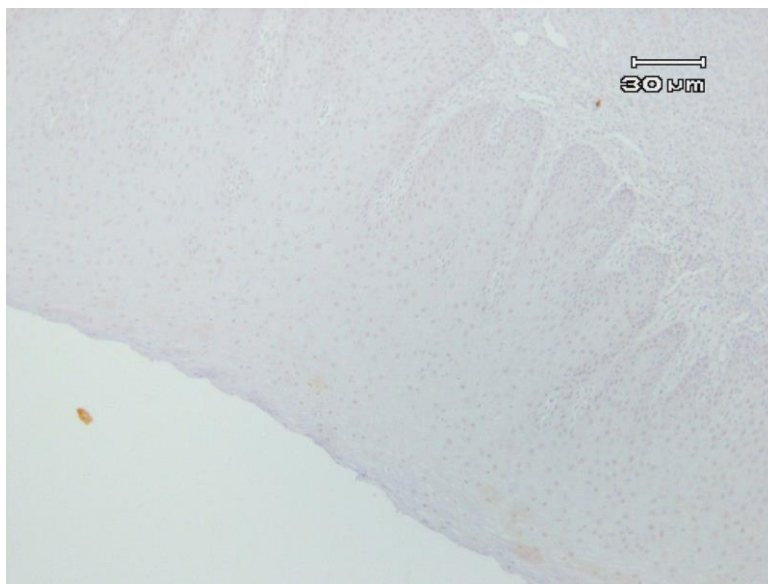


Figure 1. HC staining of ER, magnification: 40x, severity of staining: 1, Percentage of staining:1

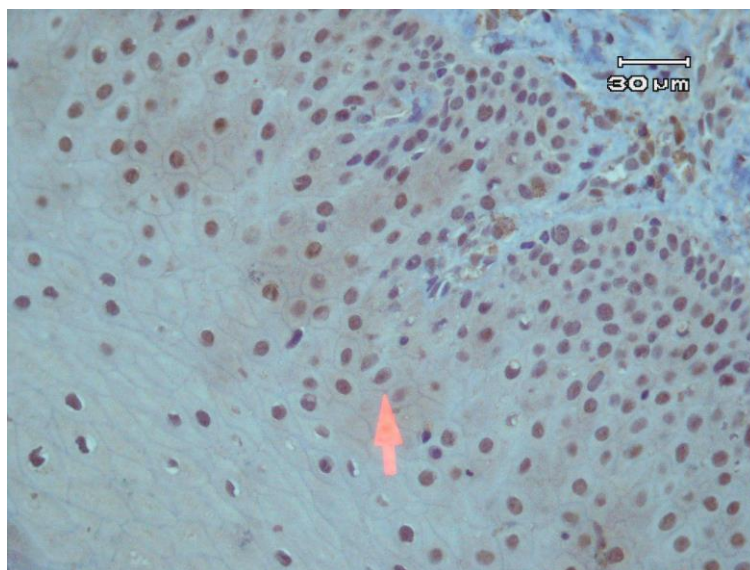


Figure 2. IHC staining of ER, magnification: 100x, severity of staining: 2, Percentage of staining: 2.

The expression of estrogen receptor percentage (ERP) in the menopausal women is higher in the control group. However, the percentage of estrogen receptor expression is higher in the non-menopausal women with lichen planus (Table 1, Figures 1 & 2).

The expression of progesterone receptor severity (PRS) is higher in the menopausal women in the control group. However, the severity (qualitative assessment) of progesterone receptor expression is higher in the non-menopausal women with lichen planus (6.3% intermediate) (Table 1, Figures 3 & 4).

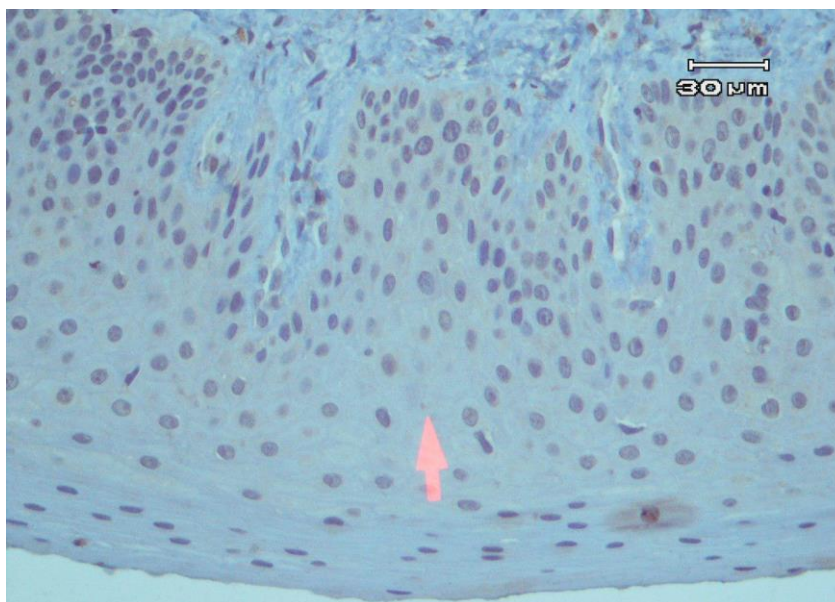


Figure 3. IHC staining of PR, magnification: 100x, severity of staining: 3, Percentage of staining: 3.

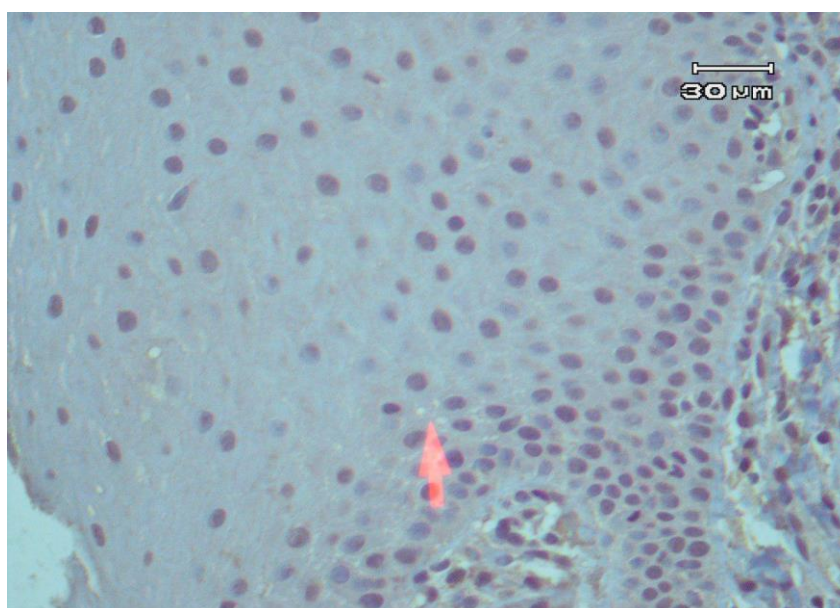


Figure 4. IHC staining of PR, magnification: 100x, severity of staining: 2, Percentage of staining: 2.

The expression of progesterone receptor percentage (PRP) is higher in the menopausal women in the control. However, the percentage of progesterone receptor expression is higher in the non-menopausal patients with lichen planus (Table 1, Figures 3 & 4).

The severity and percentage of expression of estrogen and progesterone receptors were higher in the non-menopausal women with lichen planus compared to other groups.

A comparison of the participants' mean scores showed no significant difference in expression of ERS, ERP, PRS, and PRP receptors in the healthy non-menopausal women,

menopausal OLP women, non-menopausal OLP women, and healthy menopausal women (Table 1).

A comparison test of the mean expression of different receptors between the case and control groups has been shown in

Table 2. As can be seen, there were no significant differences in the expression of ERS, ERP, PRS, and PRP in the healthy non-menopausal women, menopausal women with OLP, non-menopausal women with OLP, and healthy menopausal women.

Table 2. Comparison of means of expression of different receptors between control and case groups

	Null Hypothesis	Test	Sig	Decision
1	The distribution of ers is the same across categories of groups	Independent-Samples Kruskal-Wallis Test	.864	Retain the null hypothesis
2	The distribution of erp is the same across categories of groups	Independent-Samples Kruskal-Wallis Test	.885	Retain the null hypothesis
3	The distribution of prs is the same across categories of groups	Independent-Samples Kruskal-Wallis Test	.618	Retain the null hypothesis
4	The distribution of prp is the same across categories of groups	Independent-Samples Kruskal-Wallis Test	.606	Retain the null hypothesis

Asymptotic significances are displayed. The significance level is .05

Discussion

Hormones mediate changes in target cells by binding to specific hormone receptors. The prolonged exposure to hormones at abnormal levels leads to the upregulation and downregulation of the expression of receptors via a feedback system (9,10). The results of this study showed that the expression of estrogen and progesterone receptors was very low in the oral mucosa of healthy individuals and OLP patients.

The expression of estrogen and progesterone receptors was low in non-menopausal women in the control group and high in the menopausal women in the control group. This finding is consistent with a hormone-receptor feedback system. The increased levels of hormones during perimenopause lead to the downregulation of receptor levels. However, the decreased levels of hormones during menopause lead to the upregulation of receptors. The feedback system seemed malfunctioning in

the OLP case-group and the expression of receptors increased in the non-menopausal case-group and decreased in the menopausal case-group. Nevertheless, this increase and decrease were not significant in both groups (1). Both oral mucosa and changes in the immune system are involved in the pathogenesis of OLP. Following the changes in the expression of antigens at the surface of oral mucosal keratinocytes, nonspecific immune mechanisms (the activation of mast cells, neutrophils, neoangiogenesis, and increased oxidative stress), and specific immune mechanisms (T-cell-mediated and B-cell-mediated) lead to the necrosis of oral mucosal keratinocytes (11-13).

Estrogen and progesterone receptors have been found on both immune cells and in different parts of the oral mucosa such as gingiva, fibroblasts, periodontal ligament osteoblasts, and lamina propria fibroblasts (14). Very low levels of the expression of estrogen and progesterone receptors in oral mucosa of the OLP patients and healthy individuals in the present study suggest that the effect of estrogen and progesterone hormones in the oral mucosa may be due to a mechanism other than binding to specific receptors, or the anabolic products of these hormones may have very specific receptors in oral mucosa. Leimola-Virtanen *et al.* showed that the assessment of estrogen and progesterone receptors in mucosal buccal cytology during menstruation and menopause was not a powerful factor for the pathogenesis of oral diseases since immunohistochemistry analysis could not detect estrogen receptors (15).

Various studies on pyogenic granuloma (PG), mucocutaneous carcinoma (MEC), acinic cell carcinoma (ACC), and central giant cell granuloma (CGCG) patients also showed that estrogen and progesterone receptors

cannot be involved in the development of the diseases (16-18). However, some studies have confirmed that the expression of these receptors is involved in oral lesions including PG, peripheral giant cell granuloma (PGCG), peripheral ossifying fibroma (POF), epulis fissuratum, and squamous cell carcinoma (SCC) (19, 20). Given these controversial findings, the effects of sex hormones and their receptors on immune system cells might be more pronounced than oral mucosa in the pathogenesis of oral mucosal diseases (especially autoimmune diseases including OLP).

The increased levels of sex hormones and high levels of receptors exacerbate the effect of high levels of these hormones on the immune system in non-menopausal OLP patients. High levels of estrogen have immunosuppressive effects on the cellular immune system and immunostimulatory effect on the humoral immune system. Since estrogen receptors are not directly found on B lymphocytes, the differentiation of B lymphocyte by reducing IL-6 and IL-7 and increasing the conversion of Th1 to Th2 is mediated by estrogen. Also, estrogen increases secretion of vascular endothelial growth factor (VEGF) involved in the pathogenesis of OLP (1, 21, 22). Similarly, high levels of progesterone in the non-menopausal period have immunosuppressive effects on the cellular immune system, especially cytotoxicity through CD8+ T-cell. However, high levels of hormone induce the mast cell infiltration and angiogenesis, stimulate the differentiation and action of B cells through binding to the GR receptor (a receptor found at the surface of most immune cells), and induce Th2 and Treg (23). This confirms that nonspecific immune mechanisms (neoangiogenesis) and B-cell-mediated specific immunity in the non-menopausal period have a more noticeable role in the pathogenesis of OLP compared to the cellular immune system.

Low levels of sex hormones and low levels of receptors in menopause in OLP patients exacerbate the effects of these hormones on the immune system.

Low levels of estrogen in menopause have stimulatory effects on the cellular immune system, increased production of inflammatory cytokines, MMPs, free radicals of oxygen and nitrogen, adhesion molecules, and reduced anti-inflammatory cytokines. Low levels of estrogen can also stimulate humoral immunity and antibody production (2). In addition to estrogen, low levels of progesterone in menopause also have a strong stimulatory effect on the cellular immune system, and the enhanced activity of oxidative stress is also involved in pathogenesis of OLP (24-26). Progesterone at the lower levels tends to bind to IPRs and MPRs receptors. MPRs receptor stimulates the differentiation and action of B cells. It is found in reproductive and non-productive systems (23). Therefore, non-specific mechanisms (the increased levels of MMPs and adhesion molecules) and specific mechanisms (through lymphocyte B cells and especially cytotoxic T-lymphocytes) seem to be involved in the incidence and exacerbation of OLP in postmenopausal periods.

The results of this study showed that autoimmune disease leads to a maladaptive hormone-receptor feedback system, which may lead to the development and exacerbation of the disease in premenopausal, menopausal, and postmenopausal periods through various mechanisms. Yih showed that estrogen receptors were expressed in the mucosa of eight patients with desquamative gingivitis among 10 OLP patients (17). The former was a cross-sectional study, not a case-control study. The effect of menopause on OLP was also not considered in the former study. Greenstein also showed the impaired structure and dysfunctioning of estrogen receptors as well as the

impaired estrogen priming of progesterone receptors in patients with systemic lupus erythematosus (SLE). These results were consistent with the results of this study. High levels of estrogen increased the production of anti-dsDNA antibodies in these patients. The production of autoantibodies against ER- α is also involved in the pathogenesis of the disease through changes in T-cell homeostasis (28).

Another study also showed high levels of the expression of ER α and ER β receptors in patients with severe psoriasis. It was shown that estrogen reduced inflammation in psoriasis through estrogen receptors in epidermal keratinocytes. Multiple sclerosis (MS) is a T helper cell (CD4 T cell)-mediated autoimmune disease characterized by chronic inflammation involving the central nervous system (CNS) (29). High levels of estrogen and progesterone have an immunosuppressive effect on the cellular immune system and reduce the symptoms and severity of the disease. ER α receptor polymorphism was also detected in these patients (30, 31). A relationship was found between ER- α receptor polymorphism and the age of onset of rheumatoid arthritis. Another relationship was found between ER- β polymorphism and the severity of the disease. Another study showed that ER- α agonist reduced IL-6 levels and prevented the disease in an animal model. However, the efficacy of ER- α and ER- β in oral diseases was not reported in other clinical trials (32-35).

Therefore, increased knowledge on the presence and distribution of hormonal receptors and their effect on the oral mucosa and immune system not only helps to understand the pathogenesis of various diseases but also contribute to gaining new insights on the prevention and treatment of these diseases.

Conclusion

Low levels of estrogen and progesterone receptors in oral mucosa of OLP patients can indicate the more pronounced role of receptors on the surface of immune cells than mucosal cells in the pathogenesis of the disease. The maladaptive receptor-hormone feedback system in OLP patients is also involved in the incidence and exacerbation of the disease by different mechanisms.

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The protocol of the study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC1395.1137).

Conflict of interests

There is no conflict of interest.

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