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Frequency of oral Lichen Planus among hypothyroid patients

Frequência de Líquen Plano oral em pacientes com hipotireoidismo

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ABSTRACT

Objective: Recent investigations have suggested a correlation between thyroid diseases, particularly hypothyroidism (HT), and oral lichen planus (OLP). **Objective:** This study aimed to assess the frequency of OLP in HT patients. **Material and Methods**: This analytical descriptive study evaluated 100 HT patients including 94 females and 6 males, who were selected by convenience sampling. The subjects were clinically examined for OLP. The mean age of patients was 42.49±1.29 years. Also, 100 age- and sex-matched healthy controls were examined. The data were analyzed using chi-square test and Fisher's exact test via SPSS. **Results**: Of all, 14 (14%) HT patients (12 females and 2 males) had OLP while only one case of OLP was found in the control group. The difference between the two groups in the frequency of OLP was significant (P=0.001). The odds ratio (OR) of developing OLP was calculated to be 16.11 in HT patients. Reticular form was the most common type of OLP in patients (50%). The buccal mucosa was the most common site of involvement (92.85%). The mean age of patients with OLP was 42.93±1.29 years with a median of 46±1.29 years in HT group. **Conclusion**: The frequency of OLP was significantly higher in HT patients such that HT patients had higher odds of developing OLP by 16 folds.

KEYWORDS

Hypothyroidism; Oral lichen planus; Frequency; Comparison.

RESUMO

Objetivo: Investigações recentes sugeriram uma correlação entre doenças da tireoide, particularmente hipotireoidismo (HT), e líquen plano oral (LPO). **Objetivo:** Este estudo teve como objetivo avaliar a frequência de LPO em pacientes com HT. **Material e Métodos:** Este estudo descritivo analítico avaliou 100 pacientes com HT, incluindo 94 mulheres e 6 homens, selecionados por amostragem por conveniência. Os indivíduos foram examinados clinicamente para LPO. A média de idade dos pacientes foi de 42,49 ± 1,29 anos. Além disso, foram examinados 100 controles saudáveis pareados por idade e gênero. Os dados foram analisados usando o teste do qui-quadrado e o teste exato de Fisher via SPSS. **Resultados:** De todos, 14 (14%) pacientes com HT (12 mulheres e 2 homens) tiveram LPO, enquanto apenas um caso de LPO foi encontrado no grupo controle. A diferença entre os dois grupos na frequência de LPO foi significativa (P = 0,001). A razão de probabilidade de desenvolvimento de LPO foi calculado em 16,11 em pacientes com HT. A forma reticular foi o tipo mais comum de LPO nos pacientes (50%). A mucosa bucal foi o local de acometimento mais comum (92,85%). A média de idade dos pacientes com LPO foi de 42,93 ± 1,29 anos, com mediana de 46 ± 1,29 anos no grupo HT. **Conclusão:** A frequência de LPO foi significativamente maior em pacientes com HT, de modo que os pacientes com HT tinham maior chance de desenvolver LPO em 16 vezes.

PALAVRAS-CHAVE

Hipotireoidismo; Líquen plano oral; Frequência; Comparação.

INTRODUCTION

Lichen planus (LP) is a non-infectious, inflammatory, mucocutaneous disease that can affect the skin, hair, nails and mucosa. Its prevalence varies from 0.5% to 2.2% in different populations, and it has a peak incidence at the age range of 30 to 60 years with a female to male ratio of 2:1. Oral lichen planus (OLP) is a type of LP that has a chronic course and a higher prevalence in females [1,2].

Lichen planus (LP) is a premalignant condition with less than 1% risk of malignant transformation. Its malignant transformation commonly occurs in the tongue lesions. Its signs and symptoms include pain, severe bleeding during toothbrushing, esthetic problems in case of gingival involvement and intolerant to spicy foods, especially in ulcerative and erythematosus types [3].

The etiology of OLP is unknown, but many factors such as immunologic disorders that affect the lamina propria and squamous cell layer of the epithelium, immunologic factors, hypersensitivity reactions to medications and amalgam, vaccines, viral infections such as HCV, HSV, EBV and HPV, autoimmune diseases such as Sjogren's syndrome and lupus erythematosus and thyroid diseases are believed to be correlated with OLP [3-5].

Clinical differentiation of OLP from other similar oral lesions is difficult. Definite diagnosis can be made by biopsy and histopathologic examination, which is not always helpful. In some cases, patients' medical history and other systemic symptoms may help in clinical diagnosis [3].

Recent investigations have focused on thyroid function in OLP patients. Noticing a higher prevalence of hypothyroidism (HT) in OLP patients compared to its prevalence in general population without OLP suggested an association between thyroid diseases especially HT and development of OLP [3-10]. HT is a type of thyroid malfunction that occurs following a reduction in level of thyroid hormones. It often occurs as a primary condition (decreased function of the thyroid gland), but can also occur secondarily (decreased activity of the pineal gland or hypothalamus) or resistance of cell surface receptors to thyroid hormones. Also, iron deposition in the thyroid gland decreases its ability to produce hormones and leads to HT. The prevalence of HT is 4.8% among the Iranian males and 12.8% among the Iranian females [11]. It is diagnosed by clinical examination and thyroid function tests. In primary HT, the thyroid stimulating hormone (TSH) increases while T4 decreases; whereas, in secondary HT, both TSH and T4 decrease [12].

The prevalence of OLP is high in patients with thyroid problems and there is no strong evidence confirming the association of thyroid autoimmune diseases such as Hashimoto's disease and OLP. In fact, in the majority of autoimmune diseases of the thyroid gland, chronic inflammation may lead to development of OLP [9].

The serum level of anti-TG and anti-TPO in Hashimoto's disease has been reported to be over 90%. In a study on Chinese patients with OLP, anti-TG and anti-TPO were detected while the patients did not have any autoimmune disease. Recently, levamisole was used by OLP patients with high serum level of anti-TG and anti-TPO. By a reduction in serum level of anti-TG and anti-TPO, the symptoms of OLP improved. These findings indicate similar mechanism of involvement in HT, which is the main and most important pathogenesis in a group of OLP patients [8].

Evidence shows high level of serum antinuclear antibody, anti-gastric parietal cell, antithyroglobulin and anti-thyroid microsomal autoantibodies in OLP patients compared to healthy controls, which suggest an association between autoimmune diseases of the thyroid gland and OLP [13-14]. On the other hand, the prevalence of HT has been reported to be higher in OLP patients compared to healthy controls [6]. Environmental factors such as infection and xenobiotics play an important role in pathogenesis of HT. Similarly, for OLP, B and T lymphocytes in cell-mediated immunity have been suggested to play a key role in HT. No explanation has been given for the comorbidity of OLP and Hashimoto's disease but they seem to have the same immunologic and pathologic processes [10].

Although previous studies have reported higher incidence of HT in OLP patients and suggested a possible correlation between the two, higher odds of HT patients in developing OLP compared to general population have not been evaluated. Considering the complications of OLP, its risk of malignant transformation, absence of a definite treatment, side effects of its symptomatic treatment and related high costs early diagnosis of OLP and its prompt management seems

necessary. In this regard, higher frequency of OLP in HT patients and a possible role of HT as a predisposing factor for OLP, enables clinicians take a step forward in timely diagnosis and management of OLP.

Meanwhile, immunologic disorders were considered as one of the predisposing factors of OLP so this study aimed to assess the frequency of OLP in HT patients based on the hypothesis of a possible relationship between occurrence of OLP and hypothyroidism.

MATERIAL AND METHODS

Study design

This study had a descriptive, analytical design with a control group. Data were collected by clinical examination of the oral cavity (observation) and blood test.

Sample selection

Subjects presenting to the endocrine clinic of Taleghani Hospital and Oral and Maxillofacial Medicine Department of Shahid Beheshti University of medical sciences Tehran, Iran in 2018-2019 were evaluated. Patients with HT whose diagnosis had been confirmed by an endocrinologist, were under follow-up for a minimum of one year and had no history of graft versus host disease or intake of medications with a risk of lichenoid reactions were enrolled [15].

Given that the primary estimate of the prevalence of OLP was 0.09 in HT patients and 0.01 in healthy controls, 100 participants were required as the minimum sample size in each group to find a difference with 8% power and $\alpha = 5\%$.

Examiner training and calibration

First, a training session was held for the examiner by an oral and maxillofacial medicine specialist regarding the clinical diagnosis of OLP lesions of different types, by means of PowerPoint presentations. The examiner, who was a senior dental student, was also instructed on how to fill out the date form after clinical examination of patients. The final clinical examination and diagnosis of patients with OLP were repeated by an oral and maxillofacial medicine specialist who was also a faculty member of Shahid Beheshti University of Medical sciences, School of Dentistry.

Eligibility criteria

The diagnostic criteria for OLP were clinical appearance of reticular, popular, plaque-like, bullous, erythematous or ulcerative lesions [15]. Van Der Meij et al. [15], in 2003 modified the World Health Organization criteria for the diagnosis of OLP and stated that erosive, atrophic, bullous and plaque-like clinical types are only considered as subgroups of OLP when they are accompanied by reticular lesions [16,17]. Also, according to Lavaee, in case of simultaneous presence of several clinical manifestations in one patient, the more severe form is considered as the main clinical manifestation of OLP [13].

The control group included subjects presenting to Shahid Beheshti School of Dentistry with no systemic disease, and matched the patient group in terms of age and sex. After obtaining written informed consent forms, they were examined and the findings were recorded.

Clinical data collection

All patients presenting to the endocrine clinic of Taleghani Hospital with confirmed diagnosis of HT who signed the written informed consent forms were subjected to oral clinical examination for detection of OLP using a disposable dental mirror, a wooden stick, sterile gauze and a spotlight. In case of presence of a lesion suspected for OLP, the patient was referred to Oral Medicine Department of Shahid Beheshti University of Medical sciences, School of Dentistry for further assessments. In addition, patients presenting to the Oral Medicine Department with a history of HT and were under regular follow-up by their physician (particularly in the past year) underwent oral clinical examination for detection of OLP. In order to confirm the diagnosis of HT, the patients' latest blood test in the past year and the dosage of levothyroxine consumed by the patient were evaluated and recorded [18]. Biopsy was performed in suspected clinical cases. In other cases, the diagnosis of OLP was confirmed by an oral medicine specialist. Patients with OLP requiring treatment were informed and referred (Figure 1).

Non clinical data collection

Data sheets were filled out for all patients. The plasma level of T4 and TSH according to the last blood test of patients (within the past year)

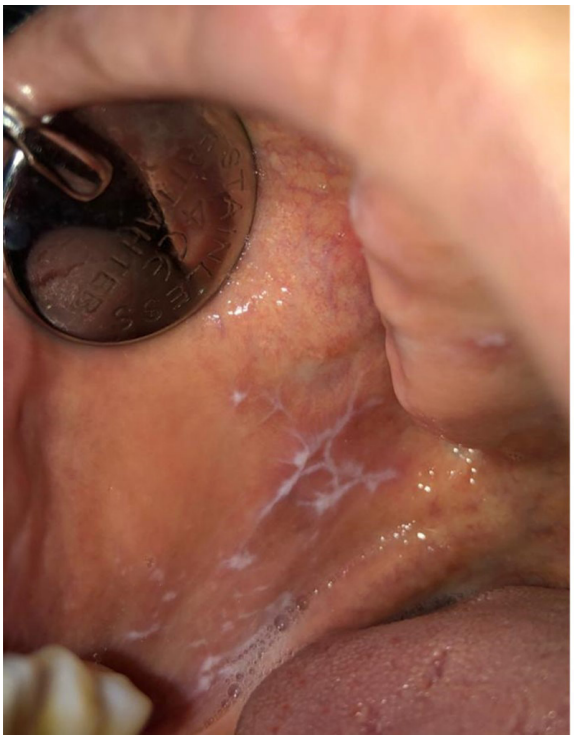

Figure 1 - Intraoral lesion of lichen planus.

and their type of medication (if any) and its dosage were also recorded. Patients who had normal TSH and T4 levels due to regular use of levothyroxine were recorded as euthyroid [18]. Patients whose test results (TSH and T4) indicated primary HT (increased TSH and decreased T4 levels) or secondary HT (decreased TSH and T4 levels) despite regular intake of levothyroxine or without it were considered as HT patients [12,18].

Data analysis

The prevalence of OLP in HT patients and healthy controls was analyzed using SPSS. Qualitative data were analyzed using the chi-square test and Fisher's exact test. $P<0.05$ was considered statistically significant.

Ethical considerations

Patients were informed about any oral and dental lesions, infections and malignancies. They also received oral hygiene instructions. The study was approved in the ethics committee of Shahid Beheshti University of medical sciences (R.SBMU.RIDS.rec.1395.36).

RESULTS

A total of 200 subjects including 100 HT patients (6 males and 94 females) and 100 age- and sex-matched controls with no systemic disease (6 males and 94 females) were evaluated. The mean age of patients was 42.49±1.29 years (range 18 to 74 years). The mean age of controls was 42.63±1.29 years (range 17 to 75 years). The two groups were not significantly different in terms of the mean age ($P=0.9$).

Table I - Frequency of OLP in HT patients and healthy controls

Group	OLP		Total
	+	-	
HT group	14	86	100
	14%	86%	100%
Control group	1	99	100
	1%	99%	100%
Total	15	185	200
	7.50%	92.50%	100%

P=0.001; Test: Chi Square.

Of 100 HT patients, 14 (14%) had OLP while 86 did not have OLP (86%); whereas, only one patient had OLP in the control group (1% OLP, 99% healthy). The difference between the two groups in frequency of OLP was significant ($P=0.001$). Also, the odds ratio (OR) of OLP in HT patients was calculated to be 16.11. The results are presented in Table I.

The female/male ratio in OLP patients was 6:1 (12:2) in the HT group. Only one female patient had OLP in the control group.

All 14 patients with OLP used levothyroxine. Of 100 HT patients, 23 (23%) had other systemic diseases as well, the most important of which were diabetes mellitus, hypertension and high serum cholesterol level.

Bilateral ulcerative lesions in the hard palate of a HT patient were diagnosed to be discoid lupus erythematosus by an oral medicine specialist. A lesion was found in the buccal mucosa of another patient, which was biopsied and found to be white sponge nevus.

Of 14 HT patients with OLP, none of them had any cutaneous lesion. Also, none of the patients were aware of their OLP. Eight patients (57.14%) were asymptomatic and 6 (42.85%) reported occasional oral mucosal burning. The buccal mucosa was the most commonly involved site (92.85%). Table II presents the frequency distribution of the site of OLP in HT patients. OLP in 7 HT patients had a reticular form (50%).

Table II - Characteristics of OLP in HT patients

Variable		Frequency	Percentage
Clinical type	Ulcerative/ erythematous	6	42.85
	Reticular	7	50
	Plaque-like	1	7/15
Location	Buccal	13	92.85
	Gingiva	4	28.57
	Tongue	3	21.42
	Lip	2	14.28
Burning sensation and pain	Yes	6	42.85
	No	8	57.15
Gender	Male	2	14.28
	Female	12	85.72

Also, ulcerative/erythematous lesions were noted in 6 patients (42.85%). Of patients, only 1 had plaque-like OLP (7.15%). The mean age of HT patients with OLP was 42.93±1.29 years with a median of 46±1.29 years.

DISCUSSION

Considering the high prevalence of thyroid diseases, particularly HT in OLP patients [5,9], this study assessed the frequency of OLP in HT patients. The results showed that the prevalence of OLP was 1% in healthy controls, which was within the normal range of prevalence of OLP in the general population (0.5% to 2.2%) [2]. However, the frequency of OLP in HT patients was 14%. The difference in this respect was significant between the two groups. This finding confirmed the association of HT and OLP, which had been previously reported by Garcia-Pola [8], Robledo-Sierra [6,7] and Siponen [5]. They assessed this association by evaluating the status of thyroid, diseases, particularly HT, in OLP patients while in the present study, we examined HT patients for OLP. No previous study has used this methodology.

Our results were in contrast to those of Lavaee [13], which may be due to the fact that the criterion for presence/absence of HT was patients' self-report when completing the patient records. Also, patient records were completed by different examiners. Despite the high number of samples, risk of errors was also high. Moreover, they did not evaluate any medical records to confirm the presence of HT in patients. The OR of OLP in HT patients was 16.11. In other words, HT can be considered as a possible predisposing factor for OLP. The OR of OLP in HT patients was 2.99 in the study by Robledo-Sierra et al. [7], 3.27 in the study by Garcia-Pola [8], 2.39 in the study by Siponen and 1.74 in the study by Lavaee [13]. These values indicate that although in our study HT significantly increased the OR of developing OLP, HT alone cannot be considered as a risk factor for OLP and other factors may also play a role in its occurrence.

In the present study, 100% of OLP patients in HT group used levothyroxine. This finding was in agreement with that of Garcia-Pola [8], Robledo-Sierra [6,7], Hirota [18] and Kragelund et al. [19]. Other studies did not report any information regarding the use of levothyroxine. Levothyroxine has not been reported to cause lichenoid reactions. Considering the fact that in this study, similar to previous ones, OLP patients regularly used levothyroxine, there is a possibility that levothyroxine may be responsible for development of OLP. Two groups of medications are commonly used by OLP patients including thyroid medications and non-steroidal anti-inflammatory drugs. Levothyroxine is the only recognized medication among the thyroid medications that is related to OLP. These findings suggest that both levothyroxine and HT may play a role in the etiology of OLP [8]. Also, high intake of thyroid medications by OLP patients has been confirmed by Siponenl [5] and Hirota [18]. The correlation between OLP and HT might be due to use of medications such as Levothyroxine by HT patients [8].

Among [14] OLP patients in HT group, the reticular form was the most common type seen in 7 patients (50%) followed by ulcerative/ erythematous type in 6 patients (42.85%). One patient (7.15%) had plaque-like OLP. This finding was in agreement with the results of Scully and Dupin [20], Farhi [21] and Alrashdan [16] regarding the high prevalence of reticular, ulcerative/erythematous and plaque-like forms in OLP patients. However, Robledo-Sierra et al. [7] reported that OLP lesions in HT patients were clinically more severe.

Based on the current findings, the frequency of OLP in HT patients was significantly higher than that in healthy controls that means HT patients had 16 times higher odds (chance) of developing OLP than normal population.

CONCLUSION

Based on the results from this research, the frequency of OLP in hypothyroid patients was high. Also, it was shown that the hypothyroid patients are 16 times more prone to have oral lichen planus.

Limitation and suggestions

Despite the high prevalence of HT in the Iranian males and females, finding HT patients for this study was difficult since such patients are not often hospitalized and are treated as outpatient. On the other hand, the majority of studies on the association of OLP and HT focused on finding HT in OLP patients. However, our methodology was different, which complicated reaching our sample size. Moreover, our results and their interpretations cannot be well compared with those of previous studies. Further studies are required on a larger sample size to find more accurate results. Furthermore, untreated HT patients should be evaluated for OLP to assess the effect of levothyroxine on development of OLP.

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Author Contributions

Maryam BAHARVAND:Concept,Supervision on data gathering and scintific writing.

Shahzad GHOLAMI:Data gathering and writing of draft.

Parisa HAJIGHASEM:Writing and correction of article.

Farzane HAMRAHI: Data gathering.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of:IR.SBMU.RIDS.REC.1395.362.

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