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Original Article

Association between vitamin D deficiency and oral lichen planus as a precancerous lesion

Maryam Jalili Sadrabad[1], Hadise Rohani[2], Fariba Yahyaei[2], Raheb Ghorbani[3,4], Shabnam Sohanian[5*]

[1]Oral and Maxillofacial Medicine Department, Dental School, Semnan University of Medical Sciences, Semnan, Iran
[2]Student Research Committee, Dental School, Semnan University of Medical Sciences, Semnan, Iran
[3]Social Health Factors Research Center, Semnan University of Medical Sciences, Semnan, Iran
[4]Department of Epidemiology and Biostatistics, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran
[5]Oral and Maxillofacial Pathology Department, Dental School, Semnan University of Medical Sciences, Semnan, Iran

*Corresponding Author: Shabnam Sohanian, Email: dr.sh.sohanian@gmail.com

Abstract

Background: Vitamin D is a pro-steroid hormone with multiple systemic functions, including immune system regulation. The effect of serum levels of this vitamin on the progression of several illnesses, including oral cancer and psoriasis, has been reported. This study investigated the prevalence of vitamin D deficiency in patients with oral lichen planus (OLP), an autoimmune disease and precancerous lesion.

Methods: This case-control study was conducted on 30 healthy individuals and 30 patients with OLP. The serum levels of vitamin D were measured by ELISA (enzyme-linked immunoassay), and vitamin D amounts lower than 10 ng/mL, 10 to 29 ng/mL, and 30 to 100 ng/mL were considered deficient, insubstantial, and adequate, respectively. Data were analyzed by Shapiro-Wilk, student's *t*-test, chi-square, and logistic regression using SPSS 24.0 software.

Results: According to the results, 36.7% ($n=11$) of patients and 43.3% ($n=13$) of the control group had vitamin D deficiency. In logistic regression analysis, the association between OLP and vitamin D deficiency was insignificant (OR=0.71, 95% CI : 0.23–2,20, $P=0.548$). Also, the correlation between age and vitamin D deficiency was insignificant (OR=0.96, 95% CI : 0.91–1.00, $P=0.061$), but the relationship between gender and vitamin D deficiency was significant (OR=4.2, 95% CI : 1.4–13.1, $P=0.013$), with a 4.2-fold higher chance of vitamin D deficiency in women compared to men.

Conclusion: The current study did not reveal a substantial correlation between vitamin D deficiency and OLP. Therefore, it seems that more studies considering the type and duration of lichen planus and a higher number of samples are necessary to evaluate the function of vitamin D in the pathogenesis of OLP.

Keywords: Vitamin D, Lichen planus, Oral, Vitamin D deficiency, Mouth neoplasms, Precancerous conditions

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Introduction

Oral lichen planus (OLP) gets its name from the Greek-Latin word lichen, which refers to a primitive plant formed from the relationship between fungi and algae, and "planus," a Latin word meaning flat.[1] This name reflects the flat, lacy appearance of the lesions associated with OLP.[2] This inflammatory disease, which affects mucous membranes, nails, the skin, and the scalp, can rarely become malignant.[3,4] Oral lesions may occur in any area of the oral mucosa but are more common in the buccal mucosa, gingiva, and the dorsal surface of the tongue and is usually seen as symmetrical and bilateral lesions in the oral mucosa.[5]

The pathogenesis and etiology of lichen planus are not entirely understood. Numerous pathological mechanisms are considered for OLP, which vary from changes in cell structure to extensive metabolic disorders. The most important theory of the incidence of OLP involves cellular immunity and its disorders.[6,7] White and red components can be seen in the clinical appearance of this lesion, which can appear in the form of bullous, reticular, plaque-like, erythematous, papular, and ulcerative lesions.[8] Treatment modalities for symptomatic patients are challenging. A variety of patients are resistant to drugs, so many routine protocols could fail.[9,10]

Vitamin D is a lipid-soluble steroid hormone that enters the body through two methods: the internal source, which involves the effect of ultraviolet rays of sunlight on the skin, and the external source, which is provided by eating foods containing this vitamin.[11] The Serum level of 25-hydroxyvitamin D is considered a valid measure of the status of this vitamin.[12] Vitamin D receptors are

abundant in T lymphocytes and macrophages and often exist in the immature thymus and T lymphocytes, mature CD8+(cluster of differentiation 8).[13] Given that epidemiological evidence demonstrates a substantial association between vitamin D deficiency and the incidence of autoimmune diseases,[1,14] the objective of the current study was to assess serum levels of vitamin D in patients diagnosed with lichen planus and examine if there is a significant relationship between vitamin D deficiency and OLP, the occurrence of lichen planus, which is one of the precancerous conditions in the body, can be prevented by either preventing vitamin D deficiency or the timely treatment of this disorder.

Methods

This study was conducted by reviewing the archive of the Oral and Maxillofacial Medicine

Department, Semnan Dental School from 2011 to 2017 and clinical examination of the patients referred to the department.

Sample selection

Thirty patients with OLP who were referred to Semnan Dental School were chosen as the case group, and 30 healthy volunteers from the same center were entered into the study as the control group. Persons who had a recurrence of the condition, as well as those with a history of taking supplements or vitamin D, were excluded from the study. Patients with lichen planus based on investigation of the demographics, medical history, medications, and intraoral soft tissue examination from the archive files from 2011 to 2017 were included in the study. Only those between 30 and 70 years old were considered. Incomplete files and individuals below 30 were excluded. Demographic data, medication related to OLP, and the type of lichen planus were recorded. Moreover, the amount of serum vitamin D was recorded if it was included in the patient's file, and blood tests were prescribed for the patients whose serum vitamin D level was unknown.

Laboratory procedure

The ELISA method was used to measure the serum level of vitamin D. For this purpose, 96 ELISA kits for anti-vitamin D3 from BYREX Fars Company were used. According to the reference values provided in the company's catalog, the following classifications were established: less than 10 ng/mL indicated vitamin D deficiency, 10 to 29 ng/mL denoted insufficient levels of vitamin D, 30 to 100 ng/mL was considered adequate vitamin D level, and levels exceeding 100 ng/mL were classified as vitamin D toxicity.[15] In this vitamin D calibration method, the patient or control samples were first added to the wells, which were coated with vitamin D antibodies, and after that, the diluent solution was added to the wells to isolate the carrier proteins from the vitamin D molecules. After the incubation and washing steps, the dye was produced by adding the substrate. The prominence of the produced dye was inversely associated with the concentration of vitamin D in the sample. A wavelength-concentration activity curve was plotted using several standards with known vitamin D levels and measured using an unidentified sample concentration curve.

All standards, samples, and control kits were first brought to room temperature (18–25 °C) before use and were used only once. Then, 25 µL of each control, standard, and serum sample was prepared according to the kit instructions and added to the wells. Following this, 75 µL of the sample's diluted solution was added to all wells. The wells were agitated using a plate shaker for 20 seconds at a speed of 200–400 rpm, followed by incubation at room temperature for 60 minutes. Subsequently, the supernatant was discarded, and the wells were rinsed three times with 350 µL of 1X buffer. After that, 100 µL of the vitamin D-conjugated enzyme solution was added to each well and incubated for 15 minutes at 25–28 °C (room temperature). The supernatant was discarded, and the wells were washed thrice with 350 µL of 1X buffer. Following this, 100 µL of the prepared substrate solution was added to each well and incubated for an additional 15 minutes in the dark at room temperature. In the final step, 100 µL of the stop solution was added to each well, and the optical density of vitamin D was measured at 450 nm. The serum levels of vitamin D in each sample were subsequently determined.

Data analysis

Data were evaluated using the Shapiro-Wilk (to evaluate normality), student's t (to compare the mean age of two independent groups), and chi-square (to assess the homogeneity of sex distribution of two independent groups) tests and the logistic regression method (to evaluate the simultaneous relationship of study variables with vitamin D deficiency) at a 0.05 level of significance.

Results

According to the findings, 56.7% ($n=17$) of patients and 53.3% ($n=16$) of the control group were female. There was no statistically significant difference in the distribution of sexes between the two groups ($P=0.795$). The mean ± standard deviation of the age was 48.9 ± 12.9 years in the patients and 48.4 ± 12.3 years in the control group, which did not have a significant difference ($P=0.467$) (Table 1). The lowest and highest ages were 29 and 70 years in patients and 24 and 72 years in the control group, respectively.

The findings show that 36.7% ($n=11$) of the patients and 43.3% ($n=13$) of the control group exhibited vitamin D deficiency. In the control group, 9 individuals (30%) had vitamin D deficiency, while 15 individuals

Table 1. Mean ± SD of age and sex distribution among oral lichen planus (OLP) patients and healthy individuals

Groups	N	Age (Mean ± SD)	*P* value	Sex		*P* value
				Male No. (%)	Female No. (%)	
OLP+	30	48.9 ± 12.9	0.467*	13 (43.3)	17 (56.7)	0.795**
OLP-(Control)	30	48.4 ± 12.3		14 (46.7)	16 (53.3)	

*Student *t* test; ** Chi-square test

(50%) had insufficient levels of vitamin D3. The logistic regression analysis indicated that the association between lichen planus (LP) and vitamin D deficiency was not statistically significant (OR = 0.71, 95% CI: 0.23–2.20, *P* = 0.548). Additionally, the association between age and vitamin D deficiency was not significant (OR = 0.96, 95% CI: 0.91–1.00, *P* = 0.061). Conversely, the association between gender and vitamin D deficiency was significant (OR = 4.20, 95% CI: 1.35–13.10, *P* = 0.013), indicating that the likelihood of vitamin D deficiency in women was 4.2 times greater than in men (Table 2).

Table 2. Relationship between OLP, gender, and age and vitamin D levels in the regression logistic analysis.

Variable	Odds ratio	95% CI for OR	*P* Value
Gender			
Female	4.20	1.35–13.10	0.013
Male	1.00	-	
Age	0.96	0.91–1.00	0.061
OLP			
+	0.71	0.23–2.20	0.548
- (Control)	1.00	-	

Discussion

This study investigated the serum levels of vitamin D in patients with OLP compared to healthy individuals. The findings indicated that the serum levels of vitamin D3 were not significantly associated with OLP. OLP is a mucocutaneous inflammatory condition attributed to various etiological factors.[16-19] The etiology and pathogenesis of lichen planus are not entirely understood; noticeably, carcinoma and dysplasia can develop in patients affected with OLP, so research about its etiologic factors is strongly recommended for the prevention of these precancerous lesions.[20,21] Vitamin D is classified as a steroid prohormone and serves as a criterion in the diagnosis of certain diseases; however, its relevance in lichen planus has been infrequently addressed in the literature.[22]

Grimm et al[22] investigated that vitamin D receptors were significantly increased in precancerous lesions and squamous cell carcinoma, but serum levels of vitamin D were low in patients who had had cancer, and there was no statistically significant correlation between serum levels of vitamin D and receptor expression. Consequently, it was stated that due to the increase in vitamin D receptors in people with squamous cell carcinoma, natural or synthetic therapeutic vitamins can be used in order to induce apoptosis in cancer cells.[23]

Beena Varma et al reported a case series of three patients with lichen planus. They declared that vitamin D deficiency has been linked to the symptoms and complications associated with OLP, and the administration of vitamin D supplements has been associated with improvements in the condition of affected patients.23 There was no significant difference between the patient group and control groups in the current study, and it was found that 39.6% and 47% of patients had a deficiency in vitamin D3 and inadequate vitamin D, respectively; these results are incompatible with the results of Thum-Tyzo et al,[24] who concluded that 84% of patients with lichen planus had vitamin D deficiency and 15% had insufficient amounts of vitamin D.[25,26]

The suppressive and regulatory effects of vitamin D on immune cells have been well established. Vitamin D influences both B and T lymphocytes, and vitamin D receptor expression is found in various immune cells, including active B and T cells, indicating a regulatory role for vitamin D within the immune system. Numerous studies have demonstrated that vitamin D deficiency, in addition to impacting bone health, is associated with several malignancies, metabolic and cardiovascular diseases, neurological disorders, and immune system disorders, such as autoimmune diseases, as well as potential weaknesses in dental tissue.[27] Vitamin D receptors can also regulate innate and acquired immune responses.[28-30]

Numerous in-vitro and in-vivo studies have shown that the most active metabolite of vitamin D is 1, 25 Dihydroxy calciferol or calcitriol. It has antiproliferative, pro-apoptotic, and anti-angiogenic properties. Combination therapy with calcitriol and a large number of cytotoxic drugs has shown it to have synergistic or at least adjuvant effects on them.[31,32]

Insufficient vitamin D levels are prevalent among the general population due to heightened use of sunscreens, increased indoor activities, and skin coverage. The results indicated that nine individuals (30%) in the control group exhibited vitamin D deficiency, and 15 individuals (50%) had insufficient levels of vitamin D3. Vitamin D deficiency within the control group may have contributed to the lack of significant difference in vitamin D3 levels between the patients and the control group. Consequently, efforts aimed at reducing the incidence of cutaneous cancer may inadvertently lead to increased vitamin D deficiency.[31]

Therefore, the incidence of OLP can also increase, and these two entities may have a potential relationship with each other.

Vitamin D deficiency is a significant concern across different age groups, and a notable inverse correlation exists between vitamin D deficiency and age. In other words, individuals over 50 are at a higher risk for vitamin D deficiency and associated diseases. Due to its lipophilic nature, vitamin D is stored in considerable quantities within body fat mass, which increases the risk of toxicity following saturation.[33]

Vitamin D deficiency arises for several reasons, such as a decrease in body fat mass and a reduced risk of accumulation, a decrease in the skin's ability to synthesize vitamin D, inadequate nutrition, and vitamin deficiency in older ages. Therefore, higher doses of vitamin can be prescribed based on serum levels of vitamin D in patients with OLP and healthy individuals.[33]

Strengths and Limitations

In order to clearly understand the role of vitamin D in OLP, it is recommended that the study be conducted with a larger sample size. Furthermore, serum evaluation of vitamin D and molecular and immunohistochemical studies of vitamin D receptors in OLP is recommended. Moreover, the examination of different types of OLP disease, pathological factors, and serum studies should be considered.

Conclusion

The present study observed no relationship between vitamin D deficiency and OLP. Therefore, it appears that further research, taking into account the type and duration of lichen planus and larger sample sizes, is necessary to assess vitamin D's role in the development of OLP.

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Authors' Contribution

Conceptualization: Maryam Jalili Sadrabad.
Data curation: Maryam Jalili Sadrabad, Shabnam Sohanian, Raheb Ghorbani.
Formal analysis: Maryam Jalili Sadrabad, Shabnam Sohanian, Raheb Ghorbani.
Investigation: Maryam Jalili Sadrabad, Hadise Rohani, Fariba Yahyaei.
Methodology: Maryam Jalili Sadrabad, Hadise Rohani, Fariba Yahyaei.
Project administration: Maryam Jalili Sadrabad.
Resource: Maryam Jalili Sadrabad.
Software: Raheb Ghorbani.
Supervision: Maryam Jalili Sadrabad, Shabnam Sohanian, Raheb Ghorbani.
Validation: Maryam Jalili Sadrabad, Shabnam Sohanian, Raheb Ghorbani.
Visualization: Maryam Jalili Sadrabad, Hadise Rohani.
Writing-original draft: Hadise Rohani, Fariba Yahyaei.
Writing-review & editing: Maryam Jalili Sadrabad, Shabnam Sohanian, Raheb Ghorbani.

Competing Interests

This study has no conflict of interest.

Data Availability Statement

Data is available at a reasonable request to the corresponding author via email (dr.sh.sohanian@gmail.com).

Ethical Approval

Confidentiality of participants' data was observed, and a written consent form was obtained from the participants; furthermore, the patients were given a sufficient explanation of the procedure, cause, and necessity of the study. The ethical code (IR.SEMUMS.REC.1398.020) was issued by the Ethics Committee of Semnan University of Medical Science.

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