Original Article
Middle East Journal of Cancer; October 2023; 14(4): 530-536

Vitamin D Serum Levels in Oral Lichen Planus and Oral Cancer Patients

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Please cite this article as: Tangarpoor M, Khademi B, Mardani M, Malekzadeh M, Jaafari-Ashkavandi Z. Vitamin D serum levels in oral lichen planus and oral cancer patients. Middle East J Cancer. 2023;14(4):530-6. doi: 10.30476/mejc.2023.95276.1762.

Abstract

Background: This study aimed to evaluate serum vitamin D levels in patients with oral lichen planus (OLP) and oral squamous cell carcinoma (OSCC) in comparison to healthy controls in an Iranian population.

Method: A cross-sectional study was conducted, which included 69 patients with OLP, 40 patients with OSCC, and 60 healthy controls. Serum vitamin D levels were measured using the ELISA method. The data were analyzed using Mann-Whitney and T-tests, and statistical significance was set at $P < 0.05$.

Results: The study found that 17.9% of OLP patients, 27.25% of OSCC patients, and 25% of the control group had normal vitamin D levels. The mean vitamin D level in OLP patients (17.00 ± 14.16 ng/mL) was significantly lower than that in the control group (22.99 ± 14.46 ng/mL) ($P = 0.003$). However, in OSCC patients, the mean vitamin D level (24.63 ± 16.19 ng/mL) was not significantly different from that of the control group.

Conclusion: The study revealed a high rate of vitamin D deficiency and insufficiency in OLP, OSCC, and control group patients. Vitamin D deficiency was more common in patients with OLP. Vitamin D deficiency may potentially increase the risk of OLP and OSCC development and progression.

Keywords: Neoplasms, Lichen Planus, Oral, Vitamin D, Serum

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Introduction

Oral lichen planus (OLP) is a common muco-cutaneous disorder that is considered a premalignant condition with an unknown etiology. Although some studies have shown the role of the immune system and some predisposing factors in its pathogenesis1, the exact cause remains unclear. Studies have

Received: April 20, 2022; Accepted: April 17, 2023

reported that 1%-2% of OLP lesions transform into oral squamous cell carcinoma (OSCC), and the frequency of malignant transformation of OLP is between 0.4% and 5%.[2]

OSCC accounts for more than 90% of all oral cancers, with tobacco usage being the principal risk factor. Other risk factors include socioeconomic status, genetic predisposition, and so forth. A diversity of endogenous and exogenous stimuli leads to a complex series of molecular changes that participate in cancer development.[3]

1, 25-dihydroxy vitamin D3 [1,25(OH)2D3] is the active form of vitamin D3, a fat-soluble vitamin that is synthesized in the skin from exposure to sunlight by UV light-mediated modifications. This vitamin is involved in the pathogenesis of several autoimmune, inflammatory, and cancerous diseases. In several studies, vitamin D has shown antiproliferative and pro-differentiation properties in a number of normal and cancer cells.[4] It affects and regulates the immune system cells and acts as an anti-inflammatory agent. Moreover, vitamin D contributes to the induction of apoptosis, inhibition of invasiveness, and angiogenesis in several human cancers[4] and has shown growth-inhibitory effects on oral cancer cell lines.[5] Additionally, calcitriol has been found to enhance the effectiveness of cytostatic chemotherapy to induce apoptosis in OSCC cells.[6]

Vitamin D deficiency has been correlated with some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, and it has shown potential therapeutic effects on some autoimmune diseases.[7] Several studies that have evaluated vitamin D serum levels in patients with OLP as well as OSCC have reported controversial results. Guta et al.[8] showed that vitamin D deficiency in OLP patients was lower than in healthy subjects. Afzal et al.[9] showed that lower vitamin D levels decreased in OSCC patients, whereas Aremd et al.[10] found no change.

Although there is great interest in investigating the anticancer properties of vitamin D, few studies have explored these effects in oral precancerous lesions and oral cancer in a limited number of patients with controversial results. Other studies used vitamin D in the treatment of OLP without strong evidence of the vitamin status in patients and reported favorable results.[8] Due to the high prevalence of OLP and OSCC, it is crucial to determine the role of vitamin D in their progress and pathogenesis. The aim of the present study was to evaluate the vitamin D status in a group of OLP and OSCC patients.

Table 1. Baseline data of all groups

Groups	Mean Age ± SD	M:F
OLP (69)	55.33 ± 11.60	21:48
OSCC (40)	62.60 ± 15.53	26:14
Control (60)	51.01 ± 13.74	18:42
Control (60)	51.01 ± 13.74	18:42

OLP: Oral lichen planus; OSCC: Oral squamous cell carcinoma; SD: Standard deviation; M: Male; F: Female

Method and Materials

This cross-sectional study was approved by the Medical Ethics Committee of Shiraz University of Medical Science (IR.SUMS.Dental.REC 1399.016).

In this study, 173 serum samples were collected during 2018-2020. Specifically, there were 70 samples from patients with OLP, 43 samples from patients with OSCC, and 60 serum samples from healthy subjects. These patients were selected from individuals who referred to the department of oral medicine at Shiraz Dental School. All patients met the clinical and histopathological criteria for OLP and OSCC. Excluded patients were those who had taken complementary and vitamin D supplements within the past two months, as well as those with diseases that alter vitamin D serum levels, such as thyroid or parathyroid diseases and hyperparathyroidism, the presence of other cancers, systemic or inflammatory diseases, and cases with a history of previous anticancer treatment and disease recurrence. The healthy subjects did not have any of the inclusion or exclusion criteria. Informed consent was obtained from all study participants.

Serum vitamin D levels were measured by the ELISA test using an antivitamin D3 ELISA kit (Monobind, cat #7725-300) according to the

Table 2. Vitamin D levels in different clinical presentations of patients

Clinical presentation	Percentage	Mean of Vitamin D	*P*-value vs. control
OLP			
Keratotic	68	17.42 ± 15.55	0.01
Non-keratotic	32	16.29 ± 14.49	0.03
Stages of OSCC			
Stage 1	17.5	33.20 ± 19.58	0.21
Stage 2	32.5	22.33 ± 13.54	0.92
Stage 3	25	30.10 ± 19.30	0.29
Stage 4	25	16.13 ± 9.22	0.20

OLP: Oral lichen planus; OSCC: Oral squamous cell carcinoma

manufacturer's instructions. A 2CC blood sample was taken from each study participant and kept at -20°C in sterile tubes. Data were analyzed using the Mann-Whitney U, Kruskal-Wallis, and Pearson Chi-Square tests by SPSS 17. Statistical significance was set at $P < 0.05$.

Results

40 OSCC patients, 69 OLP patients, and 60 controls were enrolled in the study. Four cases with outlier data were removed. The mean age ± standard deviation (SD) of participants was 62.60 ± 15.53 for OSCC, 55.33 ± 11 for OLP patients, and 51.01 ± 13.74 for the controls. Baseline data of all study groups are illustrated in table 1.

Most of the OLP patients had the erosive and reticular type of OLP, and most of the OSCC patients were in stage 2 of the disease; both groups were not significantly different (Table 2).

Table 3 shows the mean vitamin D levels in all groups. The mean vitamin D levels in OLP patients (17.00 ± 14.16 ng/mL) were significantly lower than those of the control group (22.99 ± 14.46 ng/mL) by Mann-Whitney test ($P = 0.003$). In the OLP group, 70% of patients suffered from vitamin D insufficiency, which was significantly lower than the vitamin D insufficiency in the control group (46.7%) (chi-square test, $P = 0.04$). The mean vitamin D levels in females with OLP lesions were significantly lower than those in the females of the control group (Mann-Whitney test, $P = 0.004$), but this difference was not found in males ($P = 0.31$). Details are illustrated in table 4. Moreover, the Mann-Whitney test showed that no significant difference existed between the mean vitamin D levels in males with OLP lesions and the control group (17.81 ± 24.45 ng/mL) in comparison with the females (20.25 ± 16.58 ng/mL) ($P = 0.96$).

The mean vitamin D levels in both erosive (16.29 ± 14.49 ng/mL) and reticular (17.42 ± 15.55 ng/mL) types of OLP were lower than those of the control group (Mann-Whitney test, $P = 0.009$ and $P = 0.03$, respectively).

The mean of vitamin D in OSCC patients (23.8 ± 16.19 ng/mL) was not significantly different from that of the control group based on the Mann-Whitney test ($P = 0.78$). Therefore, 51.1% of OSCC patients had vitamin D insufficiency, and 23.2% had deficiency, which was not significantly different from vitamin D insufficiency (46.7%) and deficiency (28.3%) in the control group (chi-square test, $P = 0.64$).

The Mann-Whitney test revealed that the mean vitamin D levels in males and females with OSCC were not significantly different from those in healthy males and females. Moreover, the mean vitamin D levels in males with OSCC and the control group (24.51 ± 16.76 ng/mL) were not significantly different from females (21.19 ± 15.33 ng/mL) ($P = 0.88$). Details are shown in table 4. Furthermore, the vitamin D levels in the control group, OLP and OSCC patients were not related to their age (Pearson correlation, $P > 0.05$).

Discussion

In this study, the serum levels of vitamin D were evaluated in a group of patients with OLP and OSCC and compared with those of a group of healthy individuals. The findings showed a high rate of vitamin D deficiency and insufficiency

Table 3. Vitamin D mean and status in all groups

D3 level	OSCC	OLP	Control	*P*- value vs. control	
				OSCC	OLP
Mean	24.63 ± 16.19	17.00 ± 14.16	22.99 ± 14.46	0.04	0.77
Insufficiency (%)	52.5	69	46.7	0.07	0.91
Deficiency (%)	20	12.9	28.3	0.69	0.96
Sufficiency (%)	27.5	17	25	0.93	0.76

OLP: Oral lichen planus; OSCC: Oral squamous cell carcinoma

in all study groups. Vitamin D deficiency was more frequent in patients with OLP.

The study findings revealed that vitamin D deficiency was prevalent in OLP and OSCC patients, as well as in the control group. 72.5% of OSCC patients, 82.9% of OLP patients, and 75% of the control group suffered from vitamin D deficiency or insufficiency. This finding confirms the high prevalence of vitamin D deficiency in the Iranian population, which is a major health problem in Iran, especially in females.[11] Cultural and social taboos that affect life-style patterns, such as dressing habits, which limit sun exposure in females, may be a reason for vitamin D deficiency in Iran.[12]

The levels of vitamin D, as well as vitamin D sufficiency, were significantly lower in the OLP group compared with the control group. In particular, most of the OLP females and males suffered from low amounts of vitamin D, with females having significantly lower levels than the disease-free controls. Some researchers have reported similar findings.[8, 13, 14] Gupta et al. have stated that urban people, vegetarians, and middle/lower-middle socio-economic classes are more likely to suffer from vitamin D deficiency,[8] although controversial results have been reported. It has been suggested that vitamin D plays a vital role in the initiation and severity of OLP through its regulatory effect on the immune system.[8] Vitamin D deficiency results in a decrease in Th2 cell counts compared with other T cells that regulate inflammatory pathways.[15] Zhao et al.[16] have demonstrated that lipopolysaccharides downregulate the VDR expression by the keratinocytes in OLP tissue compared with normal oral mucosa. This function is dependent on the tumor necrosis factor-alpha (TNFα)-miR-346 pathway, and vitamin D/VDR could play a protective role in the integrity of oral mucosa.

In our study, mean vitamin D levels in both erosive/atrophic and reticular types of OLP were lower than control patients, which is consistent with some previous reports.[8, 13] Moreover, erosive lichen planus is associated with severe pain and burning that can be related to vitamin D deficiency in these patients.[8] Ahmed et al. have shown that vitamin D deficiency is not only related to the development of OLP but also related to the symptoms and types of OLP.[13] Studies have shown the role of vitamin D in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, asthma, and infectious diseases.[17, 18] Lack of vitamin D has been found to increase the cytotoxic activity of cells.[19]

Our findings regarding the high incidence of vitamin deficiency in OSCC patients were in agreement with previous studies. Grimm et al.[20] reported that among their 42 OSCC patients, 100% of them had moderate to severe vitamin D deficiency. Anand et al.[21] reported 76.4% deficiency among their patients, and another study reported 65% vitamin D deficiency and insufficiency in the OSCC group.[19] In this study, no significant difference existed between vitamin D levels in the OSCC and the control group. Arem's study also showed no association between serum 25(OH) D and the risk of head and neck cancers.[10] They reported a mean vitamin D level of about 31 in their study. Their patients were male smokers from the white population. In contrast, data from other studies[19, 22, 23] have shown a significant difference between the cancer and control groups. The mean vitamin D levels in our OSCC group were 24.6 ng/mL, which is in agreement with 22 and 20.4 ng/mL in previous studies.[19, 23] These results indicate that the lack

Table 4. Mean of vitamin D levels based on patients' gender

	OLP	OSCC	Control	*P*-value vs. control	
				OLP	OSCC
Female	17.16	28.93	29.68	0.004	0.59
Male	17.81	22.31	20.19	0.30	0.88

OLP: Oral lichen planus; OSCC: Oral squamous cell carcinoma

of association between vitamin deficiency and SCC development in the present study is mostly related to a high rate of vitamin deficiency among the control group. In our study, 25% of the control group had normal vitamin D levels, and this rate was 46.90% and 38% in the aforementioned studies.[10, 23]

Vitamin D and its metabolites reduce the incidence of various cancers by inhibiting tumor angiogenesis, stimulating mutual adherence of cells, and enhancing intercellular communication, thereby strengthening the inhibition of cellular proliferation.[21, 24]

In our OSCC group, the mean vitamin D levels were lower in the last stage, with no significant difference with other disease stages, which was probably due to our limited sample size of each stage. Udeabor et al.[23] have shown that vitamin D levels were decreased in the late stages of SCC. This could be because of disease severity and complications during this stage. One study has shown that in patients with different head and neck tumors, higher vitamin D serum levels were associated with better survival and progression-free survival.[25] Bochen et al.[22] found a significant association between higher vitamin D serum levels with a negative lymph node status and a possible inhibitory effect of Vitamin D on tumor cell metastasis. They also showed that vitamin D status was related to the patients' survival rate. In patients with advanced cancer stages, it has been shown that vitamin supplementation reduced therapy-related toxicities and improved the quality of life of patients.[13, 22]

A few limitations were presented in our study, similar to most of the previous research on vitamin D levels, including the lack of data about the duration of previous exposure to sunlight, BMI, number of pregnancies, and parathyroid hormone and calcium serum levels. Moreover, the final period of the study coincided with the COVID-19 pandemic, which resulted in increased vitamin D consumption among the entire population, and this factor prevented an exact gender match between the cancer and other groups.

Conclusion

In this study, there was a high rate of vitamin D deficiency and insufficiency in patients with OLP and OSCC, as well as in the control group. The mean serum levels of vitamin D in patients with OLP were significantly lower than in healthy subjects; however, the difference was not significant between OSCC patients and the control group. This could be mostly attributed to the high rate of vitamin deficiency in the control group. The results of the present study further corroborate the assertion that vitamin D deficiency may be a potential risk factor in the development and progression of OLP and OSCC. As with patients who have other immunologic disorders, vitamin D deficiency should be considered in patients with OLP and OSCC, regardless of the site and type of OLP and OSCC. Given the high attention paid to vitamin D consumption during the Coronavirus disease 2019 (Covid-19) pandemic period, further studies are suggested to compare the incidence of these disorders before and after vitamin therapy.

Acknowledgement

The authors would like to thank the Vice-Chancellorship of Shiraz University of Medical Sciences for supporting this research (Grant # 98-01-03-20846). The authors also thank Mr. Vossoughi from the Dental Research Development Centre for performing the statistical analysis. This article is related to the undergraduate thesis of Dr. Maryam Tangarpour.

Conflict of Interest

None declared.

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