ORIGINAL ARTICLE
ISSN 2645-4351
https://doi.org/10.22037/jds.v44i1.47175

Serum Level of 25-Hydroxy Vitamin D in an Iranian Subpopulation with Oral Squamous Cell Carcinoma with Different Histopathological Grades

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Submitted: 7 December 2025
Revised version received: 10 June 2026
Accepted: 21 June 2026
Published online: August 2026

How to cite:
Bakhshi M, Manifar S, Shirkhoda M, Rahimzamani A, Fahimi Nejad A, Tofangchiha M, Mofid A, Karimi A. Serum Level of 25-Hydroxy Vitamin D in an Iranian Subpopulation with Oral Squamous Cell Carcinoma with Different Histopathological Grades. J Dent Sch 2026;44(1):e20.

Abstract

Objective(s): Emerging research indicates that vitamin D may exert antioxidant properties and potentially contribute to reducing the likelihood of cancer development. Multiple studies have indicated that inadequate vitamin D status is linked to a higher incidence of certain cancers, including colorectal and breast malignancies. This study aimed to investigate serum vitamin D concentrations in patients diagnosed with oral squamous cell carcinoma (OSCC) across different histopathological grades and to compare these levels with those of healthy subjects. **Methods:** The present case–control study consisted of 40 individuals with OSCC and 40 age- and sex-matched healthy participants. Serum samples of all participants were analyzed for vitamin D concentration using the enzyme-linked immunosorbent assay (ELISA) method. The collected data were evaluated using the independent t-test and Chi-square test at $p<0.05$. **Results:** Serum vitamin D concentrations were markedly lower among patients with OSCC compared with the control group. Moreover, elevated concentrations of vitamin D were associated with a lower risk of OSCC occurrence. This inverse association reached statistical significance in patients with grade I tumors, whereas no significant relationship was observed in grades II and III. In addition, tumor site showed no significant association with histopathological grade. **Conclusion:** These findings suggest that adequate serum vitamin D levels may contribute to reducing the risk of OSCC.

Keywords: Squamous Cell Carcinoma of Head and Neck; Cancer; Histopathology; Oral; Vitamin D; Iran

Introduction

Vitamin D is a fat-soluble hormone produced in the skin following exposure to ultraviolet (UV) radiation. Beyond its essential function in maintaining calcium balance and supporting bone integrity, increasing evidence suggests that vitamin D may also contribute to the prevention and progression control of various cancers. Evidence from various studies suggests that maintaining adequate vitamin D levels through supplementation may lower the incidence of several forms of malignancy and may help inhibit tumor development and progression [1, 2].

Antioxidants are biologically active substances that counteract reactive oxygen species, thereby minimizing oxidative injury and preserving cellular and tissue function. Hormones produced within the body, including estradiol and melatonin, as well as antioxidant vitamins such as C and E, contribute to body's defense against oxidative stress. Their protective activity is attributed to their role as non-enzymatic antioxidant molecules [3].

In recent years, the antioxidant potential of vitamin D has attracted considerable scientific interest. Owing to its structural similarity to cholesterol, vitamin D has been proposed to possess antioxidant properties and may contribute to the reduction of oxidative stress within biological systems[4]. Dietary intake by itself is generally insufficient to meet body's requirement for vitamin D. Synthesis of this vitamin depends largely on exposure to UV radiation, which initiates the biochemical pathways responsible for its production in the skin. Given that exposure to sunlight is the primary natural means of vitamin D production, populations living in areas with consistent year-round sunshine would generally be expected to exhibit lower deficiency rates. Nevertheless, studies published over the past twenty years have documented a notably high occurrence of vitamin D deficiency in several countries, including Iran, China, and India, with prevalence estimates ranging from 30% to 93%. A variety of factors may contribute to this public health concern, such as geographic and environmental influences, clothing habits that reduce UV exposure, differences in skin pigmentation, and insufficient dietary intake of foods containing vitamin D [5-7].

Evidence suggests that calcitriol [$1\alpha,25(OH)_2D_3$], the hormonally active form of vitamin D, and several of its synthetic counterparts may exert anticancer effects, highlighting their potential value in tumor prevention and treatment. These effects are attributed to its ability to regulate

cellular growth, promote programmed cell death, suppress the formation of new blood vessels within tumors, and enhance the responsiveness of cancer cells to therapeutic agents by decreasing treatment resistance. Owing to these mechanisms, calcitriol has been proposed as a supportive adjunct to conventional anticancer therapies [8, 9]. Evidence from epidemiological investigations has indicated an association between inadequate vitamin D status and an increased risk of both cancer initiation and progression. This relationship has been reported across multiple malignancies, including breast, thyroid, lung, colorectal, and prostate cancers, as well as melanoma and lymphoma. These findings support the hypothesis that calcitriol may contribute to inhibition of tumor growth by limiting the proliferation of malignant cells, particularly in certain cancers such as those affecting the head and neck region [10, 11].

Over recent decades, cancer has become one of the most significant challenges to public health worldwide and remains one of the foremost causes of death worldwide. Among all malignancies, head and neck cancers account for roughly 5% of diagnosed cases, with nearly 50% originating within the oral cavity [12]. Although considerable attempts have been made to improve the clinical outcomes and increase survival among individuals with oral cancer through various combinations of standard treatment modalities, these strategies have not yet resulted in substantial improvements in prognosis [13, 14]. Consequently, there is growing interest in identifying novel therapeutic approaches and reliable prognostic biomarkers that may improve the management and outcome of these malignancies [15].

A number of investigations have identified a negative correlation between the incidence of head and neck malignancies and circulating levels of specific vitamins, a finding largely attributed to the potent antioxidant capacity of these compounds. By neutralizing free radicals, which are known to promote carcinogenesis, these micronutrients contribute to cellular protection and maintenance of tissue integrity. Furthermore, vitamins and carotenoids participate in several biological processes relevant to cancer prevention, including the induction of programmed cell death, suppression of excessive cellular proliferation, and stimulation of DNA repair pathways. They are also essential for maintaining normal cellular differentiation and tissue homeostasis [16, 17]. Furthermore, ecological and population-based studies suggest that people who experience greater exposure to UV radiation from sunlight tend to have a reduced likelihood of developing several forms of cancer [18]. On the other hand, Hossein et al.[19] reported a positive association between serum vitamin D concentration and the occurrence of skin cancer, proposing that vitamin D status may serve as an indirect indicator of cumulative exposure to UV radiation. Janbabai et al.[20] reported that reduced serum vitamin D concentrations were significantly related to more advanced disease status, larger tumor dimensions, and higher histopathological grades among individuals diagnosed with breast cancer.

Considering the clinical significance of vitamin D and the scarcity of research examining its potential role in prevention and progression of oral cancers in Iranian population, additional investigations are warranted to clarify this relationship [19]. Accordingly, the present study was designed to assess and compare serum vitamin D concentrations between patients with oral squamous cell carcinoma (OSCC) of varying histopathological grades and healthy control subjects.

Methods

2.1. Patients

The study sample consisted of individuals diagnosed with OSCC who were admitted to the Cancer Institute of Imam Khomeini Hospital, Tehran, Iran. Enrollment was carried out following surgical treatment and prior to the initiation of radiotherapy. Eligible participants were adults aged 18 years and older with a diagnosis of OSCC confirmed through histopathological examination. Patients who had consumed vitamin D supplements during the month preceding the study inclusion were excluded to avoid potential confounding effects on serum vitamin D measurements.

Patients who had other cancer types, had started chemotherapy or radiotherapy, had renal disease, and pregnant and lactating women were excluded from the study. Additionally, people diagnosed with vitamin D or calcium deficiency by a physician or according to their paraclinical tests were excluded. Healthy controls were also selected who were over 18 years of age, had no systemic disease, and had not received any vitamin D supplementation in the past month. The patients were enrolled by convenience sampling until the sample size was reached. According to α=0.05 and β=0.2 and SD = 6, a minimum of 14 samples were required in each group. Accordingly, the final sample size was increased to 40 in each group. The case and control groups were frequency-matched with respect to age and sex to minimize potential confounding effects. Information regarding the histopathological grading of each tumor was extracted from the patients' clinical records and systematically documented for subsequent analysis. Tumors were categorized according to the following grading system [21, 22]:

Grade I (G I): Neoplasms exhibiting a high degree of cellular differentiation and classified as low-grade lesions.

Grade II (G II): Tumors showing moderate differentiation and regarded as intermediate-grade lesions.

Grade III (G III): Neoplasms with limited differentiation, corresponding to high-grade tumors.

Grade IV (G IV): Undifferentiated malignancies characterized by the highest degree of aggressiveness and included within the high-grade category.

The research protocol received ethical approval from the

Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RIDS.REC.1395.395). Prior to inclusion in the study, written informed consent was obtained from all participants. Moreover, all stages of the investigation were conducted in full compliance with the applicable ethical principles, institutional requirements, and relevant regulatory guidelines.

2.2. Procedure

At first, 5mL of the patients' blood was collected by a nurse. Then, the blood samples were centrifuged, and serum was separated by the standard laboratory procedure. The serum samples were refrigerated, and finally, all collected samples were transferred to a laboratory for measurement of serum vitamin D levels. The same was performed for the control group. The level of serum vitamin D was measured by the "PadtanGostarIsar" kit (Iran), via the ELISA technique (Elisys Uno HUMAN, Wiesbaden, Germany) according to the absorbance spectra, and reported in nanograms per milliliter (ng/mL). The used kit was based on competitive ELISA, and the microplates were coated with anti-vitamin D antibodies. The kits had an equal number of plates for the test and control groups, and after incubation at a suitable temperature, biotin-labeled vitamin D competed with endogenous vitamin D to bind to the anti-vitamin D antibody binding sites. Finally, concentration of vitamin D in the samples was indirectly measured proportionally to light absorbance at 450 nm.

Assessment of vitamin D status is typically based on measuring circulating levels of 25-hydroxycholecalciferol [25(OH)D], which is considered the most dependable indicator of vitamin D availability in the body [23]. In this investigation, a serum vitamin D value ≥35 ng/mL was regarded as indicative of an optimal status. Participants were then grouped according to established vitamin D deficiency thresholds using the classification criteria presented below [24]:

Mild deficiency: serum vitamin D concentration ranging from 25 to 35 ng/mL

Moderate deficiency: serum vitamin D concentration between 12.5 and 25 ng/mL

Severe deficiency: serum vitamin D concentration of 12.5 ng/mL or lower

2.3. Statistical analysis

All statistical procedures were completed with SPSS software (version 21). Vitamin D levels were reported as means and standard deviations for both patients and controls. Group differences were assessed using an independent t-test. Logistic regression approaches, including multinomial models, were applied to estimate odds ratios and examine potential associations between vitamin D status and the variables under investigation. Furthermore, the relationship between histopathological grading and tumor location was analyzed using Chi-square statistics. All tests were performed at a significance level of 0.05.

Results

3.1. Participants: The investigation included a total of 80 participants, consisting of 40 individuals diagnosed with OSCC and 40 healthy subjects who were matched to the patient group with respect to age and sex.

3.2. Demographics: Table 1 compares the age and gender between the patient and control groups. The analysis demonstrated that the patient and control groups were comparable in terms of average age and gender, with no significant difference detected between them (P=0.21 and P=1.00, respectively).

3.3. Serum level of vitamin D: As shown in Table 1, serum vitamin D concentrations differed significantly between the two groups. The patient group demonstrated lower mean vitamin D levels than the control group, with an observed difference of 3.63 units that reached statistical significance (P = 0.016).

Table 1- Comparison of demographic factors and serum level of vitamin D in patients with OSCC and healthy controls

Factors		Control (N = 40)	OSCC (N = 40)	P-value
Gender	Male	20 (50 %)	20 (50 %)	1
	Female	20 (50 %)	20 (50 %)	
Age		58.93±10.6 (range 30 to 78 years)	60.39±8.52 (range 40 to 77 years)	0.210
Serum level of vitamin D (ng/mL)		28.38 ± 6.83	24.75 ± 6.39	0.016

3.4. Association of serum level of vitamin D and histopathological grade: Table 2 presents the results of multinomial logistic regression. The control group served as the baseline, and the three histopathological grades were compared with the control group. Grade IV patients were not evaluated due to unavailability of such samples. As vitamin D levels increased, the probability of OSCC decreased, suggesting a protective relationship between adequate vitamin D status and disease occurrence. The observed association reached statistical significance specifically among cases classified as Grade I OSCC.[OR= 0.89; 95% CI: 0.81-0.98; P = 0.026). As shown, each 1 ng/mL increase in vitamin D was associated with an 11% reduction in the odds of having grade I OSCC (i.e., OR = 0.89). However, this association was not significant for grades II and III.

3.5. Association of tumor location and histopathological grade: Table 3 shows the location of tumors based on their histopathological grade. As shown, tumor location and grade were not significantly correlated (P=0.409).

Table 2- Association of serum level of vitamin D and histopathological grade of OSCC compared with the control group

Grade	serum level of vitamin D (ng/mL)	OR (95% CI)	P-value
Control group*	28.38 ± 6.83	1	-
OSCC grade I	23.98 ± 6.66	0.89 (0.81, 0.98)	0.026
OSCC grade II	26.22 ± 7.99	0.95 (0.86, 1.04)	0.295
OSCC grade III	23.90 ± 5.19	0.89 (0.79, 1.02)	0.088

* Reference level
OR: Odds ratio; CI: Confidence interval

Table 3- Location of OSCC in the oral cavity according to its histopathological grade

Location	Total (N = 40)	Histopathological grade N (%)			P-value
		I	II	III	
Tongue	20 (50%)	8 (44.4%)	8 (57.1%)	4 (50.0%)	0.409*
Buccal mucosa	10 (25%)	4 (22.2%)	4 (28.6%)	2 (25.0%)	
Lower lip	5 (12.5%)	3 (16.7%)	2 (14.3%)	0 (0%)	
Upper lip	2 (5%)	2 (11.1%)	0 (0%)	0 (0%)	
Floor of the mouth	3 (7.5%)	1 (5.6%)	0 (0%)	2 (25.0%)	

* Based on the Monte Carlo simulation

Discussion

Enhancing the apoptosis of tumor cell precursors is a key factor for prevention and treatment of cancer [25]. Natural or artificial vitamin D has been proposed to induce apoptosis, and plays a role in cancer treatment [26, 27]. Researchers believe that induction of apoptosis by using vitamin D in pre-cancerous lesions such as leukoplakia and lichen planus, and tumors may be useful to prevent their malignant transformation. Also, it may be useful as an apoptosis-sensitizing agent in OSCC treatment planning [27]. Moreover, antioxidants have a vital role in reducing the oxidative stress and harmful effects of reactive oxygen species on amino-acids, proteins, and DNA molecules in the human body [28]. Vitamin D may be considered as an antioxidant due to its structure [4].

In the present study, serum vitamin D concentrations were assessed in individuals diagnosed with OSCC of varying histopathological grades and subsequently compared with those measured in healthy participants. A significant difference in serum vitamin D status was observed between the groups, with individuals diagnosed with OSCC exhibiting lower mean vitamin D levels than those in the control group. In addition, an inverse association was observed between vitamin D levels and OSCC risk, with increasing vitamin D concentrations corresponding to a decreased likelihood of disease occurrence. This inverse relationship reached statistical significance in patients with grade I tumors; however, no significant association was detected in grade II or grade III lesions. Additionally, tumor site was not significantly related to histopathological grade. The lack of significant findings in some analyses may be due to the relatively small sample size, highlighting the need for future studies involving larger cohorts to more accurately investigate these relationships.

Zhang et al.[29] proposed a novel molecular mechanism involved in human SCC tumorigenesis, along with a pharmacological mechanism describing the anticancer effects of $1,25(OH)_2D_3$ in human SCC. They also highlighted an interesting paradox whereby UV radiation, despite being carcinogenic, may simultaneously exert a protective effect during the early phases of SCC carcinogenesis.

Grimm et al.[24] explored vitamin D status in individuals diagnosed with OSCC by measuring serum vitamin D concentrations and analyzing VDR expression in premalignant oral lesions as well as cancerous oral tissues. Their findings suggested that promoting apoptosis in VDR-expressing cells through the use of natural or synthetic forms of vitamin D could represent a promising strategy for cancer prevention. In addition, they proposed that vitamin D, administered either orally or topically, may increase the susceptibility of tumor cells to radiotherapy and chemotherapy, thereby enhancing treatment-induced apoptotic responses in OSCC [24]. Meyer et al.[30] examined the relationship between dietary vitamin D consumption, serum concentrations of biologically active vitamin D, and several clinical endpoints, including cancer recurrence, occurrence of second primary malignancies, and overall survival, among patients with stage I and II head and neck cancer before the initiation of radiotherapy. Although numerous earlier investigations suggested that vitamin D may have a protective role in cancer, the study by Grimm et al. [24] did not identify a significant association between pretreatment vitamin D status and either prognosis or major clinical parameters in their patient cohort. Fanidi et al.[1] examined the relationship between serum vitamin D status and both disease occurrence and survival outcomes in

patients with head and neck cancers and esophageal malignancies. Their findings indicated that reduced levels of 25-hydroxyvitamin D were associated with an increased risk of all-cause mortality among individuals diagnosed with head and neck cancer. In agreement with these findings, the present study demonstrated that patients with OSCC had significantly lower mean serum vitamin D levels compared with healthy individuals. An inverse relationship was observed between circulating vitamin D concentrations and the risk of OSCC, with higher vitamin D levels corresponding to a reduced probability of disease development. Janbabai et al.[20] reported that diminished serum vitamin D levels were significantly associated with adverse clinicopathological features among patients with breast cancer. Their findings indicated that vitamin D deficiency was correlated with more advanced stages of disease, increased tumor dimensions, and higher histopathological grades, implying that inadequate vitamin D status may contribute to a more aggressive tumor phenotype. Arem et al.[18] evaluated the association between circulating 25-hydroxyvitamin D [25(OH)D] levels and the risk of oropharyngeal and laryngeal cancers in a cohort of Finnish male smokers. Using a prospective case–control design, the study examined whether serum vitamin D status was related to the incidence and progression of head and neck squamous cell carcinoma (HNSCC). No statistically significant relationship was identified between circulating 25(OH)D levels and the likelihood of HNSCC occurrence. Atoumand et al.[31] reviewed the available evidence regarding the role of vitamin D in breast cancer. Their findings suggested a negative correlation between serum vitamin D levels and the likelihood of breast cancer occurrence, with higher vitamin D concentrations being associated with a lower risk of disease development. This observation further supports a potential protective function of vitamin D against carcinogenesis.

The results of the present study should be considered with several limitations in mind. First, the case–control nature of the study design precludes establishing a causal relationship between serum vitamin D concentrations and the progression of OSCC. Second, because no cases of grade IV OSCC were identified at the Cancer Institute of Imam Khomeini Hospital during the study period, it was not possible to assess vitamin D status across all histopathological grades of the disease. Furthermore, serum vitamin D concentrations are influenced by multiple factors, such as exposure to sunlight and dietary habits, use of vitamin D supplements, medication consumption, and lifestyle modifications associated with illness, all of which may have acted as confounding variables. The modest number of participants included in the study represents an additional limitation, as it could have affected the robustness of the statistical analyses and decreased the likelihood of detecting meaningful associations.

Future investigations with larger populations are recommended to achieve a more representative distribution of patients across different tumor stages and to provide a more comprehensive evaluation of the association between vitamin D status and disease severity. Additionally, patients with potentially malignant oral lesions showing clinical or histopathological evidence of epithelial dysplasia were not included in the present study. Assessing serum vitamin D levels in such individuals may offer further insight into the biological processes involved in the initiation and progression of OSCC. Future research should also account for major behavioral risk factors, including tobacco use and betel quid chewing, and appropriately adjust for their potential confounding effects.

Conclusion

The findings of the current investigation revealed that individuals diagnosed with OSCC exhibited significantly lower serum vitamin D concentrations than healthy participants. Higher level of vitamin D was associated with lower odds of OSCC. This association was statistically significant for grade I OSCC. These observations indicate that vitamin D may contribute to reducing the risk of OSCC development; however, its relationship with tumor differentiation status and the degree of histopathological aggressiveness has yet to be clearly established.

Acknowledgement: The authors would like to thank the laboratory staff at Imam Khomeini Hospital Complex, Tehran, Iran, and also Dr. Fatemeh Naseri Taheri for translation and Dr. Mojdeh Kalantar Motamedi for editing of this manuscript.

Author Contributions: N.F.M.: Conceptualization, Supervision, Project administration; H.A.: Methodology, Statistical analysis, Supervision; S.F.M.: Data collection, Data curation; L.F.M.: Writing – original draft, Editing; S.Y.: Writing – original draft, Editing, Statistical support.

Funding: None to declare.

Ethical Approval Code: This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (protocol code: IR.SBMU.RIDS.REC.1395.395; date of approval: 2018).

Informed Consent Statement: Written informed consent was secured from all participants before their enrollment in the study. The authors also confirm that all research procedures were conducted in full compliance with applicable ethical standards, institutional requirements, and regulations pertaining to studies involving human subjects.

Data Availability Statement: The datasets used and/or produced during the present investigation are available from the corresponding author and will be shared upon justified request.

Using AI: Artificial intelligence was not used in preparation of this manuscript.

Conflict of Interest: The authors confirm that they have no competing interests or conflicts of interest to disclose in relation to this study.

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