Low Serum 25-hydroxyvitamin D Levels in Oral Cancer Patients

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Abstract

Vitamin D is thought to have a protective role in cancer formation and development. The study aimed was to evaluate the serum 25-hydroxyvitamin D (25(OH)D) levels and their relationship with cancer stage in a cross-sectional study among oral cancer patients.

Oral cancer was clinically diagnosed and confirmed by histopathological examination. Serum 25(OH)D levels were measured using Human 25-Dihydroxy-vitamin D ELISA Kit.

Sixty subjects were enrolled in this study, 30 oral cancer patients (66,7% women and 33,3% men) and 30 healthy control subjects (66,7% women and 33,33% men). The mean age of the oral cancer patients was 52 $\pm$ 14 years from a range of 19-78 years and the healthy control group was 34 years $\pm$ 9 years from a range of 23-55 years. 61,5% of oral cancer patients had 25(OH)D deficiency. Serum 25(OH)D levels in oral cancer patients (16.83 ng/mL) were significantly lower ($p<0.05$) compared to the healthy controls (62.90 ng/mL). Bivariate analysis revealed no significant relationship between 25(OH)D levels and cancer stage in oral cancer patients ($p>0.05$).

Our study indicated that most oral cancer patients have a deficiency of 25(OH)D levels. This finding suggests that individuals with low serum vitamin D levels may have a high risk of developing cancer.

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Introduction

Oral cancer is a malignant neoplasm that appears on the lips or oral cavity. It is traditionally defined as a squamous cell carcinoma because 90% of cancers in the area of the oral cavity histologically originate from squamous cells.[1–3]

Oral cancer ranks twelfth of the most common cancers in the world, two-thirds of the incidence of oral cancer in the world occur in developing countries.[4] It is estimated that the annual incidence is around 275,000 for oral cancer in developing countries.[5] Based on a survey conducted in 2012, it is known that there were 300,373 new cases of oral cancer, which contributed to 145,353 deaths during that year.[6] In Indonesia, oral cancer has a prevalence of 3-4% of all cancer cases with a mortality rate reaching 2-3% of all deaths due to malignancy.[5]

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The cause of oral cancer is not yet clear, this is because the causes of oral cancer are multifactorial and very complex.[5] However, several local factors act as predisposing factors for oral cancer, including poor oral hygiene, chronic irritation of tooth restoration, plaque build-up, while external factors include smoking, alcohol consumption, viruses, and customs such as chewing betel, which is still widely practiced by people in Asia, especially Southeast Asia, and the host factors themselves include gender, age, nutritional status as well as the immunological condition and genetic.[5,7–9] One of the influential nutrients is vitamin D (25(OH)D), which is thought to have a relationship with several; negative health effects such as diabetes mellitus, cardiovascular disorders and cancer.[10]

Vitamin D is a fat-soluble precursor for the calcitriol steroid hormone, which is known to have a very beneficial role in bone metabolism, calcium absorption, and immune function.

Vitamin D is thought to have a protective role in cancer formation and development.[7,11,12,13] Reduced vitamin D concentrations can increase cell proliferation, inhibit cell differentiation, and increase tissue invasion, metastasis, and angiogenesis in tumours.[14–19]

The aim of this study was to analyse the serum 25(OH)D levels and their relationship with cancer stages in oral cancer patients.

Materials and methods

This cross-sectional design was conducted at Dr. Hasan Sadikin General Hospital, the main referral hospital in West Java Indonesia. Ethical permission has been obtained from the Research Ethics Committee of Padjadjaran University No 1192/UN6.KEP/EC/2019. Data about patient's identity, diagnosis and stage of oral cancer was collected by taking anamnesis, clinical and histopathological examinations. 2 ml of blood was drawn by venepuncture technique to evaluate serum 25(OH)D levels. Serum 25(OH)D levels were measured using Human 25-Dihydroxy-vitamin D ELISA Kit (Bioassay Technology Laboratory®, Shanghai China).

The classification of 25(OH)D levels used is taken from the Endocrine Society as: deficiency <20 ng/mL; insufficiency 21-29 ng/mL; sufficiency >30 ng/mL; and toxic >100 ng/mL. The differences of serum 25(OH)D levels between oral cancer patients and the healthy control groups were analysed by chi-square test and the relationship between serum 25(OH)D levels and cancer stages using the Spearman rank test.

Results

Sixty subjects who met the inclusion criteria were enrolled in this study. The characteristics of the study subjects can be seen in Table 1. Most of the oral cancer types was OSCC and the majority of patients diagnosed in advance stages. Figure 1 showed the clinical future of the several oral cancers found in this study.

Table 2 showed that serum 25(OH)D level in patients with oral cancer was lower (16,83 ng/mL) than healthy control group (62,90 ng/mL), and statistical analysis using chi-square test revealed a strong significant difference ($p<0.05$).

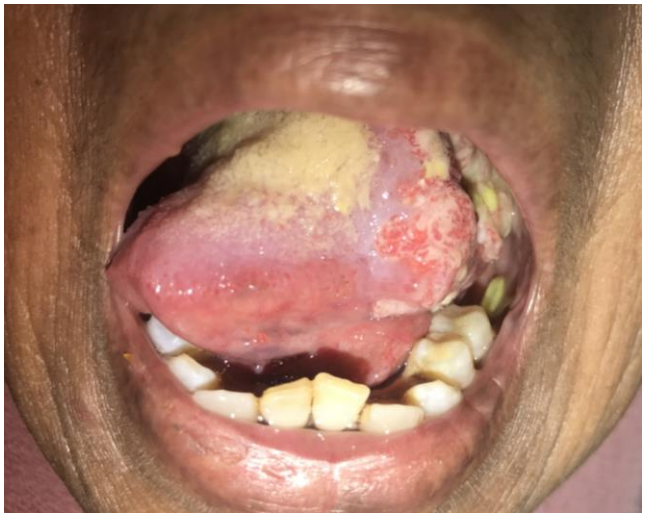

Figure A.

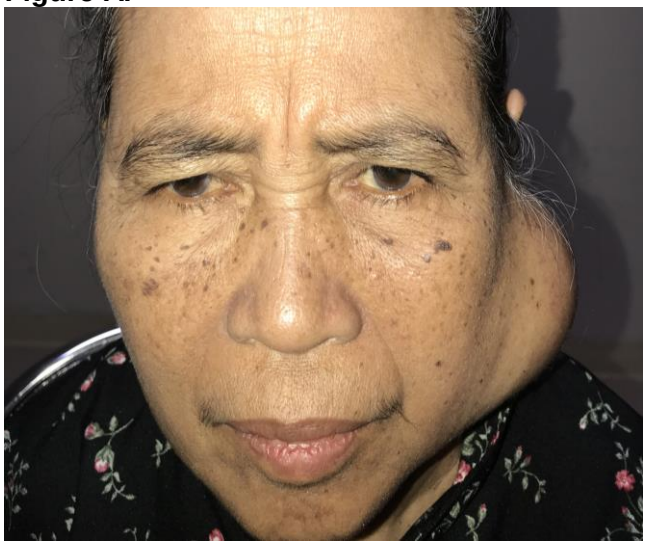

Figure B.

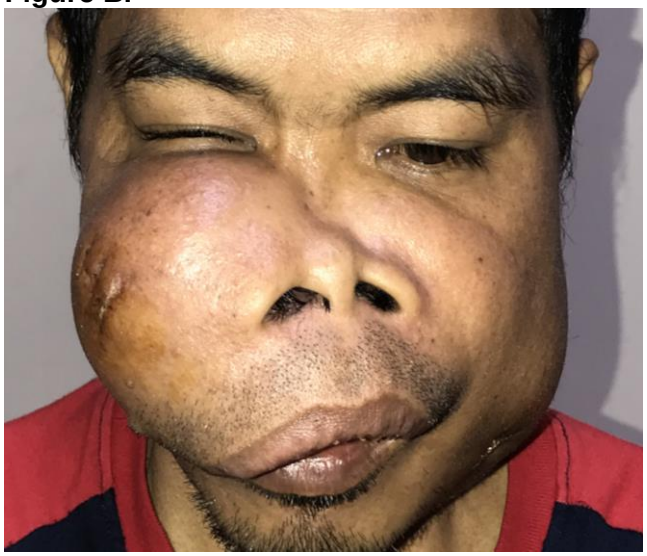

Figure C.

Figure 1. Clinical features of Oral Cancers. A. Oral Squamous Cell Carcinoma; B. Parotid Carcinoma; C. Ameloblastoma.

Variable	Oral cancer control group n=30 (patients)	Healthy n=30
Age (years), median ± SD	52 ± 14	34 ± 9
Gender, n (%)		
- Male	10 (33.3)	10
- Female	(33.3)	
	20 (66.7)	20
	(66.7)	
Occupation, n (%)		
- Retired	3 (10.0)	
- Student	1 (3.7)	
- Government employee	1 (3.7)	
- Teacher	2 (6.7)	
- Unemployed	2 (6.7)	
- Housewife	18 (60.0)	
- Entrepreneur	3 (10.0)	
Education, n (%)		
- Elementary School	15 (50.0)	
- Junior High School	3 (10.0)	
- Senior High School	8 (26.7)	
- Diploma	2 (6.7)	
- Bachelor	2 (6.7)	
Oral cancer type, n (%)		
- Squamous Cell Carcinoma	23 (76.7)	
- Parotid Carcinoma	5 (16.7)	
- Basal Cell Adenocarcinoma	1 (3.3)	
- Polymorphous Adenocarcinoma	1 (3.3)	
Cancer Stage, n (%)		
- Stage I	5 (16.7)	
- Stage II	7 (23.3)	
- Stage III	8 (26.7)	
- Stage IV	10 (33.3)	

Table 1. Characteristics of the research subjects.

Variable	Oral Cancer n=30	Healthy Controls n=30	P value
Serum 25(OH)D (ng/mL)			<0,001a*
- Median	16.83	62.90	
- IQR	13.52 – 25.57	31.13 – 134.70	
- Min-max	0.83 – 169.71	0.25 – 231.56	

Table 2. Comparison of serum 25(OH)D levels in oral cancer patients and healthy controls. *IQR=Inter Quartile Range, *n= quantity. *chi square.

Variable	Cancer Stage				R coefficient	p value
	Stage I n=5	Stage II n=7	Stage III n=8	Stage IV n=10		
Serum 25(OH)D (ng/mL)					0,271	0,090
- Median	14.20	18.10	17.55	18,49		
- IQR	20.23– 32.73	18.35–49.48	14.08–24.8	15.18–33.71		
- Range	13.44–34.15	0.83 – 40.04	5.30 – 54.03	0.95– 169.71		

Table 3. Profile of serum 25(OH)D level in oral cancer patients according to the cancer stage. *IQR=Inter Quartile Range, *n=quantity, *Rank spearman test.

Table 3 showed the profile of serum 25(OH)D level in every cancer stage in the study subjects, and statistical analysis using Spearman rank test revealed that there was no relationship between serum 25(OH)D level and stage of cancer stages in oral cancer patients (p>0.05).

Discussion

The results of this study were consistent with previous studies that most of oral cancer types (76.7%) were oral squamous cell carcinoma (OSCC) followed by parotid carcinoma, basal cell adenocarcinoma, and polymorphous Adenocarcinoma. A prior study also reported that the most common type of oral cancer was epithelial cancer, followed by salivary gland carcinoma, and the most common type of epithelial cancer is squamous cell carcinoma.[20] Our findings also showed that most OSCC had reached stage IV. Delay in diagnosis can generally be caused by lack of patient's knowledge about the signs and symptoms of the disease, delayed confirmation of cancer diagnosis, and system delay including constraints in the health care system, availability of resources, and the economics of health care can result in scheduling delays.[21–23]

The profile of serum 25(OH)D levels in oral cancer patients showed that most oral cancer patients (66,67%) had serum 25 (OH) D deficiency, and statistically significant difference compared to the healthy control group. This finding was in line with the prior study showing that most of the patients with OSCC had serum 25(OH)D levels moderate deficiency, whereas most the healthy control group had serum lev25(OH)D levels sufficiency.[24] It has been reported that precancerous and OSCC lesions have been shown to express receptors for Vitamin D Receptor (VDR) significantly increased compared with normal tissue.[24,25,26] It is known that VDR is capable of affecting tumour differentiation, aggressiveness, and apoptosis.[27]

Resistance to apoptosis has been known to play a critical role in the carcinogenesis of OSCC,[28] and vitamin D (calcitriol) may overcome apoptosis resistance in tumour cells of OSCC.[25] Activation of two apoptotic pathways (caspase and bcl:bax) by vitamin D is likely responsible for the anti-OSCC effect.[24,29]

Our study also revealed no relationship between 25(OH)D levels and oral cancer stages. A prior study revealed there was also no significant correlation between serum vitamin D levels and corresponding immunohistochemically detected VDR expression in OSCC.[25]

The similar results studied in another type of cancer also showed that there were no association between serum levels of 25(OH)D and cancer stage in breast cancer patients.[30] However, contradictory results found that showed an association of low levels of vitamin D with advanced stages, positive lymph node involvement, and large tumour size in breast cancer patients. These findings suggested that the prognostic effect of vitamin D might due to an

increased tumour aggressiveness in patients with low vitamin D levels.[31]

Conclusions

Our findings showed that the majority of oral cancer patients have a deficiency of 25(OH)D levels and significantly difference with the healthy control group, but there was no relationship with cancer stages. Recommendation for vitamin D supplementation for people at risk of vitamin D deficiency may benefit both in oral cancer prevention and improve the prognosis of cancer patients.

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Declaration of Interest

The authors declare that there is no conflict of interest.

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