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Research Article

Clinical Significance of Serum 25-Hydroxyvitamin D Levels in Non-Small Cell Lung Cancer

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Abstract

Objectives: Lung cancer is the most common cause of cancer-related deaths worldwide. The use of tobacco and tobacco products is among the leading risk factors with proven association with lung cancer, although various environmental and dietary factors have been also implicated. Vitamin D deficiency has been identified as a poor prognostic factor in advanced stage colon cancer and breast cancer. The aim of the present study was to compare 25-hydroxyvitamin D [25(OH)D] levels between patients with non-small cell lung cancer (NSCLC) at the time of diagnosis and healthy controls and to evaluate the differences in serum 25(OH)D levels across the subgroups and stages of NSCLC.

Methods: A total of 462 patients with NSCLC who were followed and treated in three participating centers were compared retrospectively with and age- and sex-matched 462 healthy controls who underwent testing for serum calcium, lactate dehydrogenase (LDH), magnesium, phosphorus, creatinine, and vitamin D levels in the between January 2016 and June 2018. The patients with NSCLC were further classified according to the histological subtype.

Results: The mean age was 63.46±8.86 years. The patient group was composed of 58 females (12.6%) and 404 males (87.4%). Serum 25(OH)D, calcium, LDH, and magnesium levels were significantly different between the patient and the control group (p=0.0001, p=0.0001, p=0.0001, p=0.0001, respectively). Among patients with NSCLC, serum 25(OH)D was significantly lower in patients with adenocarcinoma subtype than in patients with squamous-cell carcinoma subtype (p=0.001). There was a significant correlation between advanced stage with decreased serum 25(OH)D and increased LDH levels (p=0.0001, p=0.0001, respectively).

Conclusion: The study is the most extensive study in our region in terms of the number of participating patients. Demonstration of a difference in serum 25(OH)D levels between histological subtypes also contributes to the literature.

Keywords: Adenocarcinoma, lung cancer, squamous carcinoma; vitamin D

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Lung cancer is the most common cause of cancer-related deaths worldwide and non-small cell lung cancer (NSCLC) comprising a variety of histological subtypes such as adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma and bronchoalveolar carcinoma accounts for 80% of all patients with lung cancer.[1] The use of tobacco and tobacco products is among the leading risk factors with proven association with lung cancer, although various environmental and dietary factors have been also implicated.[2]

In recent years, there is a growing evidence from epidemi-

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ological studies suggesting an association between vitamin D deficiency and autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, and inflammatory bowel disease.[3] As it is well-known, inflammation is often associated to carcinogenesis.[4] Vitamin D influences the development of cancer through the modulation of inflammatory system by regulating cytokine levels in the microenvironment of tumor, inhibiting prostaglandins, activating mitogen-activated protein kinase phosphatase 5 (MPK5), inhibiting nuclear factor kappa B (NF-KB) signaling pathway, and inhibiting immune cells (i.e., macrophages, dendritic cells, T and B cells).[4]

Serum vitamin D deficiency has been identified as a poor prognostic factor in all gastrointestinal cancers, particularly in advanced stage colon cancer and breast cancer.[5] However, the role it plays in lung cancer still remains to be elucidated. The overall survival was found to be higher in patients with Stage I and II NSCLC who were operated in summer and who received vitamin D-fortified diet than in patients who were operated on in winter and who had poor dietary intake.[6] Zhou et al.[7] reported that high plasma vitamin D levels favorably affected survival in patients with Stage Ib and II NSCLC, although this effect disappeared in patients with advanced disease. As opposed to these data, Cheng et al.[8] found no relationship between plasma vitamin D levels and lung cancer in the US population.[8] However, there is a limited number of data regarding the relationship between vitamin D status and subtypes of NSCLC and disease stage.

Serum 25(OH)D level below 20 ng/mL is defined as vitamin D deficiency.[8] In the present study, we aimed to compare 25(OH)D levels between patients with NSCLC at the time of diagnosis and healthy controls and to evaluate the differences in serum 25(OH)D levels across the subgroups and stages of NSCLC.

Methods

This retrospective study was approved by the Pamukkale University, Non-interventional Clinical Trials Ethics Committee (Decree No: 70034/Date: October 15, 2018). The study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 462 patients with NSCLC who were followed and treated in three participating centers were compared with blood test date, age- and sex-matched 462 healthy controls who underwent testing for serum calcium, lactate dehydrogenase (LDH), magnesium, phosphorus, creatinine and vitamin D levels between January 2016 and June 2018. Inclusion criteria for patients were: histopathologically diagnosed as having NSCLC (adenocarcinoma, squamous cell carcinoma, bronchoalveolar, or large cell lung carcinoma). Who were already taking a vitamin D supplement or active vitamin D and who had a history of urinary tract stones both excluded from control and patient groups.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean and standard deviation (SD) and number and frequency. The Student's t-test was used for continuous variables and the Fisher's exact test was used for categorical variables. A p value of <0.05 was considered statistically significant.

Results

The mean age in the patient group (n=462) was 63.46±8.86 years (range, 28-85). The patient group was composed of 58 females (12.6%) and 404 males (87.4%). Histological subtypes and disease stage at the time of diagnosis are presented in Table 1. Serum 25(OH)D, calcium, LDH and magnesium levels were significantly different between the patient and the control group (Table 2). When the patients with NSCLC were evaluated according to the histological subtype, serum 25(OH)D was significantly lower in patients with adenocarcinoma than in patients with squamous-cell carcinoma (Table 3). In addition, since the number of patients in "other histology" group was less than the other groups, comparisons between the groups were made using Bonferroni corrections, with p<0.017 accepted as significant for Table 3. When the patients were evaluated according to the clinical disease stage, a significant correlation was observed between advanced stage and decreased serum 25(OH)D and increased LDH levels (Table 4).

Discussion

Experimental studies have shown that circulating 25(OH)D decreases cellular proliferation and increases apoptosis in NSCLC.[9] It has been also shown that vitamin D inhibits the growth of lung cancer metastases in experimental animal

Table 2. Histological subtypes and clinical stages of the patients

Characteristics	Patients (n)	Percentage (%)
Histology		
Adeno	171	37.0
Squamous	243	52.6
Other	48	10.4
Stage		
1	13	2.8
2	55	11.9
3	115	24.9
4	279	60.4

Table 2. Laboratory parameters of the patient and control groups

Laboratory parameters	Control		Patients		p value
	Mean±SD	Med (min-max)	Mean±SD	Med (min-max)	
Vitamin D	26.9±8.7	26.5 (11.1-66.5)	16.5±9.8	14.29 (0-91.8)	0.0001*
Calcium	9.3±0.5	9.31 (8.3-10.6)	9.5±0.8	9.4 (7.3-14.8)	0.0001*
Phosphorus	3.4±0.5	3.4 (1.42-4.78)	3.46±1	3.4 (1.4-9.2)	0.311
Lactate dehydrogenase	177.2±37.2	175 (98-480)	273.4±244.6	222.5 (100-4229)	0.0001*
Magnesium	2±0.2	1.99 (1.13-3.4)	1.9±0.3	2 (1.-3.4)	0.0001*
Creatinine	0.9±0.2	0.9 (0.5-2.3)	0.9±0.3	0.85 (0.5-2.3)	0.632

*P<0.05 statistically significant. SD: Standard deviation; Med: Median; Min: Minimum; Max: Maximum.

Table 3. Laboratory parameters of the patients according to the histological subtype

Laboratory parameters	Histology	Mean±SD	Median (min-max)	p value
Vitamin D	Adeno	15.5±10.44	13.7 (0-91.8)	0.001* (adeno-squamous)
	Squamous	16.93±8.89	15.9 (0-66.7)	
	Other	17.8±11.9	15.07 (3-70)	
Calcium	Adeno	9.43±0.61	9.4 (7.3-14)	0.103
	Squamous	9.55±0.85	9.39 (7.7-14.8)	
	Other	9.69±0.89	9.6 (7.6-13.4)	
Phosphorus	Adeno	3.51±0.97	3.4 (1.8-9.2)	0.184
	Squamous	3.4±1.05	3.4 (1.35-9.17)	
	Other	3.56±0.76	3.6 (1.6-5.6)	
Lactate dehydrogenase	Adeno	268.84±122.27	227 (134-1161)	0.084
	Squamous	273.31±308.46	214 (100-4229)	
	Other	290.48±206.82	226 (124-1297)	
Magnesium	Adeno	1.93±0.32	1.96 (1.02-3.35)	0.415
	Squamous	1.95±0.2	2 (1.3-2.62)	
	Other	1.95±0.27	2 (1.3-2.5)	
Creatinine	Adeno	0.86±0.33	0.8 (0.39-3.03)	0.252
	Squamous	0.9±0.24	0.89 (0.37-1.9)	
	Other	0.87±0.38	0.79 (0.54-2.9)	

*P<0.05 statistically significant. SD: Standard deviation; Min: Minimum; Max: Maximum.

models.[10] Furthermore, it has been demonstrated to prevent the migration of tumor cells in lung cancer by inhibiting angiogenesis.[10] Immunomodulator function of vitamin D can play a role in preventing lung cancer. In lung cancer cell lines, vitamin D upregulates the protein expression by inhibiting mammalian target of rapamycin (mTOR) activity and promotes autophagia of tumor cells.[11] In addition, it prevents the development of lung cancer by upregulating the expression of superoxide dismutase 1 and 2, the major antioxidant defense system.[12] In the light of the available data based on the experimental studies, vitamin D can be suggested to have a protective effect against lung cancer.

Chemoprevention studies in breast and colon cancer have revealed that vitamin D has an antitumor activity.[13] In a meta-analysis by Zhang et al.[14] involving 290,000 cases, high vitamin D levels were shown to reduce the risk of NSCLC. However, this meta-analysis found no relationship between high vitamin D supplementation and a reduction in the risk of NSCLC. In a meta-analysis by Liu et al.[15] reported that vitaminD-fortified diet significantly reduced the risk of NSCLC and higher serum vitamin D level significantly reduced NSCLC-related mortality. In a meta-analysis by Muller et al.[16] involving 20 prospective cohort studies, patients with lung cancer, serum vitamin D levels measured five years before the diagnosis of NSCLC did not differ from those of age, sex, blood test date, race, and smoking status-matched controls and the authors reported no relationship between serum vitamin D concentration and the

Table 4. Laboratory parameters of the patients according to the disease stage

Laboratory parameters	Stage	Mean±SD	Median (min-max)	p
Vitamin D	1	26.07±7.83	23.19 (16.6-35.3)	0.0001*
	2	22.62±13.42	21.85 (3.5-70)	
	3	19.28±10.26	18.9 (3-91.8)	
	4	14.15±7.96	12.3 (0-54.4)	
Calcium	1	9.53±0.4	9.6 (8.74-10)	0.134
	2	9.38±0.5	9.3 (8.4-10.9)	
	3	9.64±0.82	9.5 (8.3-14)	
	4	9.49±0.81	9.3 (7.3-14.8)	
Phosphorus	1	3.32±0.65	3.4 (1.75-4.1)	0.723
	2	3.36±0.52	3.3 (2.1-4.6)	
	3	3.51±0.91	3.4 (1.9-9.17)	
	4	3.46±1.11	3.4 (1.35-9.2)	
Lactate dehydrogenase	1	220±121.78	234 (157-676)	0.0001*
	2	202.07±63.42	182 (110-496)	
	3	218.29±70.24	212 (100-541)	
	4	308.07±301.27	246 (108-4229)	
Magnesium	1	1.99±0.18	2 (1.5-2.3)	0.824
	2	1.95±0.29	2 (1.1-3.35)	
	3	1.93±0.24	2 (1.3-2.5)	
	4	1.94±0.26	1.97 (1.02-3.1)	
Creatinine	1	0.87±0.19	0.86 (0.62-1.2)	0.778
	2	0.88±0.21	0.87 (0.39-1.6)	
	3	0.88±0.26	0.85 (0.37-2.03)	
	4	0.89±0.32	0.85 (0.4-3.03)	

*P<0.05 statistically significant. SD: Standard deviation; Min: Minimum; Max: Maximum.

risk of developing lung cancer. A possible relationship between vitamin D status and NSCLC still remains a hot topic attracting the attention of researchers due to conflicting results in the literature.

To date, experimental studies have evaluated the efficacy of vitamin D in various subtypes of NSCLC. Serum vitamin D suppressed the growth of tumor cells in squamous cell lung cancer, whereas it showed no effect on adenocarcinoma cell lines.[17] Similarly, vitamin D replacement study in a mouse model with squamous cell carcinoma of the lung showed that vitamin D reduced premalignant cellular proliferation, inflammation, and tumor proliferation.[18] However, the relationship between serum vitamin D status and the subtypes of NSCLC in clinical practice has not been evaluated. In our study, we found significantly lower vitamin D levels in the adenocarcinoma subgroup than in the squamous cell carcinoma subgroup. This finding can be attributed to the fact that adenocarcinoma subtype is associated with a poorer prognosis than the squamous cell carcinoma.[19] The decrease in vitamin D levels which is inversely associated with an increase in clinical stage at the time of diagnosis also supports the findings of Wang et al.[20]

In their study, Akiba et al.[21] compared patients with NSCLC who received vitamin D replacement for one year after tumor surgery with the placebo group and found no significant difference than general population in terms of progression-free survival (PFS) and overall survival (OS); however, they observed a significant increase in the PFS and OS rates with vitamin D replacement in the early-stage adenocarcinoma patients. The most recent meta-analysis of 17 prospective cohort studies involving 139,000 patients also suggested that high serum vitamin D levels played a role in the prevention of lung cancer.[22] The risk of lung cancer decreased by 8% and the risk of mortality from lung cancer decreased by 7% for every 10 ng/mL increase in serum vitamin D levels.[22]

Nonetheless, there are some limitations to this study. In the present study, we were only able to evaluate laboratory parameters at the time of diagnosis and, therefore, there is a need for long-term follow-up and survival analysis. However, the strength of our study is that, to the best of our knowledge, this is the most extensive study in our geographic region in terms of the number of participating patients. In addition, demonstration of a difference in serum 25(OH)D levels among the histological subtypes may also contribute

to the growing body of knowledge in the literature.

In this study we found serum 25(OH)D levels were significantly lower in the patient group, and serum 25(OH)D was significantly lower in patients with adenocarcinoma than the squamous cell carcinoma.

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Disclosures

Ethics Committee Approval: This retrospective study was approved by the Pamukkale University, Non-interventional Clinical Trials Ethics Committee (Decree No: 70034/Date: October 15, 2018).

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
2. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584–94. [CrossRef]
3. Liu W, Zhang L, Xu HJ, Li Y, Hu CM, Yang JY, et al. The Anti-Inflammatory Effects of Vitamin D in Tumorigenesis. Int J Mol Sci 2018 Sep 13 [E-pub ahead of print], doi: 10.3390/ijms19092736. [CrossRef]
4. Han Y, Zhang Y, Jia T, Sun Y. Molecular mechanism underlying the tumor-promoting functions of carcinoma-associated fibroblasts. Tumour Biol 2015;36:1385–94. [CrossRef]
5. Grant WB. 25-hydroxyvitamin D and breast cancer, colorectal cancer, and colorectal adenomas: case-control versus nested case-control studies. Anticancer Res 2015;35:1153–60.
6. Zhou W, Suk R, Liu G, Park S, Neuberg DS, Wain JC, et al. Vitamin D is associated with improved survival in early-stage non-small cell lung cancer patients. Cancer Epidemiol Biomarkers Prev 2005;14:2303–9. [CrossRef]
7. Zhou W, Heist RS, Liu G, Asomaning K, Neuberg DS, Hollis BW, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. J Clin Oncol 2007;25:479–85. [CrossRef]
8. Cheng TY, Neuhouser ML. Serum 25-hydroxyvitamin D, vitamin A, and lung cancer mortality in the US population: a potential nutrient-nutrient interaction. Cancer Causes Control 2012;23:1557–65. [CrossRef]
9. Nakagawa K, Kawaura A, Kato S, Takeda E, Okano T. 1 alpha,25-Dihydroxyvitamin D(3) is a preventive factor in the metastasis of lung cancer. Carcinogenesis 2005;26:429–40.
10. Nakagawa K, Sasaki Y, Kato S, Kubodera N, Okano T. 22-Oxa-1alpha,25-dihydroxyvitamin D3 inhibits metastasis and angiogenesis in lung cancer. Carcinogenesis 2005;26:1044–54.
11. Hershberger PA, Modzelewski RA, Shurin ZR, Rueger RM, Trump DL, Johnson CS. 1,25-Dihydroxycholecalciferol (1,25-D3) inhibits the growth of squamous cell carcinoma and down-modulates p21(Waf1/Cip1) in vitro and in vivo. Cancer Res 1999;59:2644–9.
12. Skaaby T, Husemoen LL, Thuesen BH, Pisinger C, Jørgensen T, Fenger RV, et al. Vitamin D status and chronic obstructive pulmonary disease: a prospective general population study. PLoS One 2014;9:e90654. [CrossRef]
13. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer 2011;128:1414–24. [CrossRef]
14. Zhang L, Wang S, Che X, Li X. Vitamin D and lung cancer risk: a comprehensive review and meta-analysis. Cell Physiol Biochem 2015;36:299–305. [CrossRef]
15. Liu J, Dong Y, Lu C, Wang Y, Peng L, Jiang M, et al. Meta-analysis of the correlation between vitamin D and lung cancer risk and outcomes. Oncotarget 2017;8:81040–51. [CrossRef]
16. Muller DC, Hodge AM, Fanidi A, Albanes D, Mai XM, Shu XO, et al. No association between circulating concentrations of vitamin D and risk of lung cancer: an analysis in 20 prospective studies in the Lung Cancer Cohort Consortium (LC3). Ann Oncol 2018;29:1468–75.
17. Higashimoto Y, Ohata M, Nishio K, Iwamoto Y, Fujimo-to H, Uetani K, et al. 1 alpha, 25-dihydroxyvitamin D3 and all-trans-retinoic acid inhibit the growth of a lung cancer cell line. Anticancer Res 1996;16:2653–9.
18. Mazzilli SA, Hershberger PA, Reid ME, Bogner PN, Atwood K, Trump DL, et al. Vitamin D Repletion Reduces the Progression of Premalignant Squamous Lesions in the NTCU Lung Squamous Cell Carcinoma Mouse Model. Cancer Prev Res (Phila) 2015;8:895–904. [CrossRef]
19. Hirsch FR, Spreafico A, Novello S, Wood MD, Simms L, Papotti M. The prognostic and predictive role of histology in advanced non-small cell lung cancer: a literature review. J Thorac Oncol 2008;3:1468–81. [CrossRef]
20. Wang X, Cui J, Gu J, He H, Li B, Li W. Plasma 25-hydroxyvitamin D deficiency is associated with the risk of non-small cell lung cancer in a Chinese population. Cancer Biomark 2015;15:663–8.
21. Akiba T, Morikawa T, Odaka M, Nakada T, Kamiya N, Ya-mashita M, et al. Vitamin D Supplementation and Survival of Patients with Non-small Cell Lung Cancer: A Random-ized, Double-Blind, Placebo-Controlled Trial. Clin Cancer Res 2018;24:4089–97. [CrossRef]
22. Feng Q, Zhang H, Dong Z, Zhou Y, Ma J. Circulating 25-hydroxyvitamin D and lung cancer risk and survival: A dose-response meta-analysis of prospective cohort studies. Medicine (Baltimore) 2017;96:e8613. [CrossRef]