

## Research Article

# Comparison of Vitamin D Levels Between Healthy Individuals and Cancer Patients

 **Aydin Aytakin**

Division of Medical Oncology, Department of Internal Medicine, Yuzuncu Yil University Faculty of Medicine, Van, Turkey

### Abstract

**Objectives:** This study aimed to determine whether vitamin D levels differ between cancer patients and non-cancer control groups, to determine the differences between the reference values and also to determine the prevalence of vitamin D deficiency in cancer patients.

**Methods:** Vitamin D levels were examined retrospectively between 2017-2018 in outpatient oncology patients and non-oncology patients who applied to Mardin State Hospital.

**Results:** A total of 355 patients were examined (157 oncologic patient group and 198 in the control group). The median age of the oncologic patient group was 55.24 (19-85) and the control group was 55.45 (18-89). The median vitamin D value of the oncology patients was 8.15 ng / mL ( $\leq 4.2$ -33.72) and the control group was 14.39 ng / mL ( $\leq 4.2$ -60.13). It was statistically significant that vitamin D levels were lower in the oncology patients when compared with the control group ( $p < 0.001$ ).

**Conclusion:** In this study, vitamin D deficiency was found to be very common in cancer patients (87.3% according to reference value of 20 ng/mL) and vitamin D levels were lower in cancer patients compared to the control group. 10 ng / mL is a suitable reference value for defining vitamin D deficiency in cancer patients.

**Keywords:** Cancer; deficiency; reference value; vitamin D

**Cite This Article:** Aytakin A. Comparison of Vitamin D Levels Between Healthy Individuals and Cancer Patients. EJMI 2020;4(2):259–264.

Vitamin D has an important role in many mechanisms in the body and can be synthesized in the body thanks to almost completely sun rays. Many genes in the immune system, bones, muscles, lungs, heart, kidney and many organs are regulated by the active form of vitamin D (1-25 (OH) Vitamin D).<sup>[1]</sup> The precursor of vitamin D, namely 25 (OH) D, is the circulating form and is considered to be the most appropriate marker to evaluate vitamin D levels.<sup>[2, 3]</sup>

Many studies have shown that there are significant relationships between vitamin D deficiency and muscle weakness, cardiovascular diseases, insulin resistance and immune sys-

tem disorders.<sup>[4, 5]</sup> In addition, there are many studies on the anti-cancer effects and growth-inhibition effect of vitamin D in cancer cells.<sup>[4]</sup>

In the 1940s, Peller<sup>[6]</sup> and Apperly<sup>[7]</sup> found the first clues for the antitumor effects of vitamin D when investigating the effects of sun exposure on cancer prevalence in American farmers and marine troops. In these studies, it was found that the incidence of skin cancer was high in individuals who were exposed to high rate of sunlight when compared with low rate of sunlight exposure (low levels of vitamin D), whereas all other tumors were found to be less frequent.

**Address for correspondence:** Aydin Aytakin, MD. Yuzuncu Yil Universitesi Tip Fakultesi, Ic Hastaliklari Anabilim Dalı, Tibbi Onkoloji Bilim Dalı, Van, Turkey

**Phone:** +90 506 972 21 07 **E-mail:** aytakxx@gmail.com, draytekin@yahoo.com

**Submitted Date:** October 10, 2019 **Accepted Date:** February 20, 2020 **Available Online Date:** March 18, 2020

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Although its primary biological activity is to regulate serum calcium levels through vitamin D receptor (VDR) and provide bone mineralization, it is also suggested to show anti-tumor properties with anti-proliferative, apoptosis, anti-angiogenesis and anti-inflammation effects.<sup>[1, 8]</sup> Several studies conducted in recent years found a correlation between vitamin D serum level and tumor incidence, and increased colorectal cancer, prostate cancer, and breast cancer risk was shown with decreased vitamin D serum level.<sup>[9-11]</sup> In addition, high vitamin D levels have been shown to be associated with increased survival in patients with breast, prostate, colorectal cancer and malignant melanoma.<sup>[12]</sup> But there are contradictions in the results of studies on the clinical effects of vitamin D deficiency in cancer patients.<sup>[13-17]</sup> There are also contradictions regarding optimal serum levels of 25 (OH) D.<sup>[18, 19]</sup> According to Endocrine Society clinical practice guideline; 25(OH)D levels were evaluated as following:  $\leq 20$  ng/mL (insufficiency), 21-29 ng/mL (deficiency) and  $\geq 30$  ng/mL (sufficiency).<sup>[18]</sup> On the other hand, some studies consider 20 ng/mL (50 nmol/L) as deficient in all individuals.<sup>[19, 20]</sup> In other studies, values below 10 ng/mL were considered as deficiency.<sup>[21, 22]</sup>

In epidemiological studies about vitamin D levels of cancer patients; these levels were reported to be less than normal values.<sup>[23]</sup> However, the reference values to be taken in cancer patients could not be determined clearly. The prevalence of vitamin D deficiency in cancer patients has been reported to vary between 14-92%.<sup>[24, 25]</sup>

This study aimed to determine whether vitamin D levels differ between cancer patients and non-cancer control groups, to determine the differences between the reference values and also to determine the prevalence of vitamin D deficiency in cancer patients.

## Methods

Vitamin D levels were examined retrospectively between 2017-2018 in outpatient oncology patients and non-oncology patients who applied to Mardin State Hospital (Internal Medicine, Physical Therapy-Rehabilitation Clinics). The control group was selected from patients with age match. Vitamin D levels were recorded at the same time period (Sunlight high times, between May-September in order to prevent seasonal differences). The demographic and clinical features of the patients were recorded retrospectively. Patients over 18 years of age were included in the study. Vitamin D levels were determined by taking 25 (OH) D measurements from peripheral blood. The device name is Advia Centaur Xp, Germany and Chemoluminance method is used to measure vitamin D levels. The first vitamin D levels were recorded. In our hospital, values below 4.2 were not

measured and the lowest values were reported as  $<4.2$  ng/mL (normal values 14-60 ng/mL). The study was approved by the local ethics committee. During the study, the principles of the Helsinki Declaration have been adhered to and attention has been given to the confidentiality of patient information.

Those with vitamin D replacement, those with parathyroid disease, those with chronic renal failure, and those with calcium-phosphate metabolism disorder were excluded from the study. Both necessary comparisons between patient and control groups and intra-group comparison in patients were aimed according to a deficiency reference value of 20 ng/mL and an insufficiency reference value of 10 ng/mL in literature.

Statistical analyses were performed using SPSS version 20.0 software. The conformity of the variables to normal distribution was analyzed by visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). Chi-Square or Fisher Exact tests were used to compare categorical variables. Parametrical variables with normal distribution; Student t-test was used for independent groups. Parametrical variables that do not meet normal distribution and ordinal variables were compared with the Mann-Whitney U test. P values less than 0.05 were considered statistically significant.

## Results

A total of 355 patients were examined (157 patients oncologic patient group and 198 patients in the control group) (features were given in Table 1). There were 111 (70.7%) female patients in the oncology group and 141 (71.2%) female patients in the control group and there was no significant difference in terms of gender ( $p=0.20$ ). The median age of the oncologic patient group was 55.24 (19-85) and the control group was 55.45 (18-89) and there was no statistically significant difference between these two groups ( $p=0.92$ ).

The median vitamin D value of the oncology patients was 8.15 ng/mL ( $\leq 4.2-33.72$ ) and the control group was 14.39 ng/mL ( $\leq 4.2-60.13$ ). It was statistically significant that vitamin D levels were lower in the oncology patients when compared with the control group ( $p<0.001$ ). When a reference value of 20 ng/mL was taken for vitamin D deficiency, a total of 257 patients (72.3%) both control and oncology patient groups had a value of  $\leq 20$  ng/mL. Of these patients, 137 (53.3%) were in the oncology group and 120 (46.7%) were in the control group. The difference between the two groups was statistically significant ( $p=0.013$ ).

When the reference value was taken as 10 ng/mL for insufficiency; 38.9% ( $n=138$ ) of the whole group had a vi-

**Table 1.** Demographic and clinical characteristics of patients

Oncologic patient group			Control group		
Age (median)	55.24		Age (median)	55.45	
Vitamin D (median) (ng/mL)	8.15		Vitamin D (median) (ng/mL)	14.39	
	<b>n</b>	<b>%</b>		<b>n</b>	<b>%</b>
Sex					
Female	111	70.7	Female	141	71.2
Male	46	29.3	Male	57	28.8
Diagnosis					
Breast cancer	72	45.9			
Colorectal cancer	29	18.5			
Genitourinary system cancer	20	12.7			
Lung cancer	12	7.6			
Gastroesophageal cancer	10	6.4			
Pancreatic-bilier tract cancers	8	5.1			
Other cancers (sarcoma, melanoma n=4, 2.5%)	4	2.5			
lymphoma	2	1.3			
Stage					
Stage 0 (DCIS: Ductal Carcinoma InSitu)	2	1.3			
Stage 1	16	10.2			
Stage 2	38	24.2			
Stage 3	27	17.2			
Stage 4	74	47.1			
Stage 4/Others					
Stage 4	74	47.1			
Out of stage 4	83	52.9			

tamin D level of  $\leq 10$  ng / mL. Of the patients with levels below 10 ng/mL, 68.8% (n=95) were oncology patients and 31.2% (n=43) were controls. The difference between the two groups was statistically significant and vitamin D insufficiency was significantly higher in oncology patients ( $p=0.006$ ).

Only when oncology patients were examined; there were 111 female (70.7%) and 46 male (29.3%) patients. Breast cancer patients were most commonly seen in the population (n=72, 45.9%); and it was followed by colorectal cancer (n=29, 18.5%), genitourinary cancer (n=20, 12.7%), lung cancer (n=12, 7.6%), gastroesophageal cancer (n=10, 6.4%), pancreatic-bilier tract cancers (n=8, 5.1%), other cancers (sarcoma, melanoma n=4, 2.5%) and lymphoma (n=2, 1.3%), respectively. The ratio of stage 4 patients was 47.1% (n=74) (Table 1).

Intra-group comparison of oncology patients according to 20 ng/mL reference value showed that; 87.3% (n=137) of the oncology patients had a value of 20 or less. When we compared Stage 4 patients with other patient groups; vitamin D values were significantly lower in stage 4 patients ( $p=0.034$ ). 93.2% (n=69) of the patients in stage 4 and 81.9% (n=68) of patients in other stages had vitamin D values of  $\leq 20$  ng/mL.

Intra-group comparison of oncology patients according to 10 ng/mL reference value showed that; 34.4% (n=54) of the patients had a vitamin D value of  $\leq 10$  ng/mL. Vitamin D level in 73% (n=54) of stage 4 patients was  $\leq 10$  ng/mL. There were no patients below this value in non-stage 4 patients and p-value was  $<0.001$ .

## Discussion

When vitamin D and cancer disease are evaluated, it is seen that 25 (OH) D values which are the indicator of serum vitamin level in individuals with cancer are lower than healthy individuals. A study by Liang Shi et al., which aimed to show that vitamin D levels are low in cancer patients, showed that 71% of 1940 individuals diagnosed with cancer have been reported to have inadequate and deficient serum 25 (OH) D levels.<sup>[26]</sup> In our study, this rate was 87.3% according to a reference value of 20 ng/mL.

As thyroid glands are an environment in which the enzymes required for VDR activation are appropriate; thyroid cancer is frequently used in clinical studies. Michael Roskies and colleagues, who first examined the relationships between thyroid cancer and vitamin D deficiency in human subjects, found significant differences between vitamin D deficiency and cancer disease.<sup>[27]</sup> In another study of patients with thy-

roid cancer, vitamin D deficiency was found more in individuals with cancerous cells. Vitamin D can not show the anti-cancer effects for various reasons such as inability to activate VDR, inadequate exposure to sunlight and this was given as an evidence of vitamin D deficiency in people with cancer.<sup>[28]</sup>

In our study, vitamin D levels were significantly lower in cancer patients compared to the control group. In a more comprehensive study showing similar features to our study,<sup>[29]</sup> long-term follow-up breast cancer patients (long term participants), patients who had diagnosis recently and healthy individuals (control group) were compared. In this study, vitamin D levels were found to be lower in patients with short-term and long-term follow-up breast cancer compared to the control group (not oncology patients). In addition, vitamin D levels were found to be lower in patients with breast cancer who were diagnosed recently when compared with patients who were under long-term follow-up and whose treatment was finished. Vitamin D levels were found to be low especially in patients who had chemotherapy. The increase in photosensitivity due to chemotherapy is held responsible for this decrease. In our study, vitamin D deficiency was frequent in stage 4 patients. This may be due to the fact that stage 4 patients who are receiving long-term chemotherapy. In this study, it was suggested that vitamin D levels may be associated with better survival and prognosis, and it was suggested that supplementation for vitamin D deficiency could be beneficial in patients receiving chemotherapy.<sup>[29]</sup>

In our study, on the basis of  $\leq 10$  ng/mL reference value, 72.5% of the total patients consisted of oncology patients group when compared with the control group and this difference was statistically significant. When only oncology patients were considered, 34.4% of the patients had vitamin D levels  $\leq 10$  ng / mL. In a South Korean study involving patients with Natural Killer lymphoma and T-cell lymphoma;<sup>[21]</sup> median vitamin D levels were 12.0 ng/mL (1.3-60.0 ng/mL) and 40% of patients had less than 10 ng / mL. These results are close to our study. In our study, vitamin D values were below 10 ng/mL in 34.4% of cancer patients and the median vitamin D value was 8.15 ng / mL in cancer patients. In this (Korean) study, vitamin D deficiency was associated with poor survival in extranodal lymphomas, but this relationship could not be demonstrated in peripheral T cell lymphomas.<sup>[21]</sup>

In our study, the deficiency was more common in stage 4 patients. Considering that these patients do not have a chance of cure, we can indirectly predict that the prognosis of cancer patients with low vitamin D levels is going to be low. In another study of Ji Riyang Kim et al., in which they

intended to demonstrate that low 25 (OH) D levels are associated with poor pathological outcomes in cancer patients, bad pathological results such as tumor mass size and proliferation of lymph nodes were found to be significantly more frequent in individuals with lower vitamin D values.<sup>[30]</sup> In a study including patients with head and neck squamous cell carcinoma; vitamin D deficiency was found to be common and had been shown to be associated with lymphatic metastasis and decreased overall survival.<sup>[31]</sup> In another study including head and neck cancers, a significant reverse correlation was found between vitamin D intake and recurrence.<sup>[32]</sup> A meta-analysis of 44165 patients with different tumors has shown that high vitamin D levels are associated with better overall survival and progression-free survival.<sup>[33]</sup> A retrospective study of 197 patients with gastric cancer revealed that the stage of gastric cancer and ratio of lymph node metastasis were inversely related to vitamin D levels. In addition, overall survival was better in patients with high vitamin D serum levels.<sup>[34]</sup> In a meta-analysis including 11 original studies and 7718 colorectal cancer patients; it was shown that high vitamin D levels were associated with better survival.<sup>[35]</sup>

In this study, vitamin D deficiency was found to be very common in cancer patients (87.3% according to reference value of 20 ng/mL). This deficiency is particularly evident in stage 4 patients. Vitamin D levels were also lower in cancer patients compared to the control group. 10 ng / mL is a suitable reference value for defining vitamin D deficiency in cancer patients. These findings suggest that vitamin D deficiency is common in cancer patients. Considering the literature examples given in the article and our study; it is obvious that more randomized controlled studies with large patient groups are needed in order to determine the role of vitamin D deficiency in cancer development, its prognostic value in cancer patients, the effect of replication of deficiency on the recurrence-progression status and survival of patients.

#### Disclosures

**Ethics Committee Approval:** Mardin Provincial Health Management. Number: 97039072-604.2. Date: 04.12.2018.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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