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Original article

Vitamin D deficiency and insufficiency in Turkish patients with breast cancer

F. Ilknur Kayalı, Rahsan Habiboğlu, İrem Sarıcanbaz
Ankara Numune Training and Research Hospital Radiation Oncology Clinic, Ankara, Turkey

Abstract. *Aim:* We aimed to reveal vitamin D levels in women with breast cancer. *Patients and Methods:* 561 women with primary breast cancer were included in the study. The median age was 55.86 years (between 20 – 78 years). All of the patients were treated with curative intend. None of the patients had metastatic disease. *Results:* The median 25(OH)D level was 11.92ng/ml and the mean 25(OH)D level was 13.91ng/ml. Deficiency was detected in 456 patients (81.28%) and insufficiency was detected in 61 patients (10.87 %). *Conclusion:* This study points out that vitamin D levels in breast cancer patients should be measured and be corrected whenever diagnosed.

Key words: vitamin D, cancer, breast cancer, women

Introduction

Vitamin D deficiency or insufficiency is more common than it is thought to be (1). Inadequate ultraviolet B (UVB) exposure, limited intake as either food or oral supplements, or bad intestinal absorbtion are the caues for deficiency (1).

When ultraviolet B (UVB) rays come into contact with the skin, cholecalciferol (D3) is formed. UVB rays have anticancer effect (2). Unfortunately 5–15% of the total average daily ultraviolet radiation (UVR) level is received by most of the people (3).

The main source of vitamin D is not only the formation of vitamin D3 from UVB rays endogenously and also oral intake by supplements and foods play role in vitamin D levels (4).

There are two biological forms of vitamin D; vitamin D2 (ergocalciferol) which is obtained from dietery sources or oral supplements, and vitamin D3 (cholecalciferol) which is obtained from ultraviolet B (UVB) (5). In the liver hydroxilation takes place to form 25(OH)D3 and then it is transported to kidneys where 1,25- dihidroxivitamin D3 (1,25(OH)2D3) and 24,25-dihidroxivitamin D3 (24R,25(OH)2D3) are produced (6). Circulating 25(OH)D level is a standart biomarker for vitamin D evaluation (7).

Exposure to solar UVB and higher 25(OH)D concentrations are important factors for survival and the mechanism how it effects cancer occurance or prognosis is well known (5). Vitamin D activates apoptosis and inhibates angiogenesis regulating multiple signaling pathways by activating vitamin D reseptor (7,8). It was proven in VITAL study that daily vitamin D can effect cancer incidence and survival (9).

Previous studies showed inverse relationship between vitamin D levels and breast cancer occurance, recurrence risk and prognosis (5). It is believed that it has an effect on aggressivines of cancer (5). As well as preclinical studies, in the health, eating, activity, and life sytle study for breast cancer it was also shown that overall survival was associated with vitamin D levels (5,6).

As not only cancer cells but most of cells have receptors for vitamin D, and deficiency may result in impaired immunity which can play a big role in response to cancer treatment (1). The active metabolite is 1,25 OHD3 which regulates the apopitosis and it is believed to have the anti-cancer activity (6,10).

Even moderate Vitamin D supplementation and increased UVB exposure can decrease breast cancer risk. Vitamin D also plays role in inhibiting estrogen synthesis in breast cancer cells. Not only in reseptor positive patients but also in reseptor negative patients, vitamin D effects apopitosis via estrogen dependent mechanisms (11). Vitamin D level effects both disease free survival and overall survival in breast cancer patients (7). It was shown that lower the vitamin D levels lower the survival rates (7,9,10), this statement was proven by several meta-analyses studies (12).

Today, the most appropriate parameter showing the status of vitamin D is considered to be 25OHD (13). Vitamin D deficiency is defined as serum hydroxyvitamin D levels less than 50nmol/L (20 ng/ml) and insufficiency as 50-75 nmol/L (20-30 ng/ml) by World Health Organization (12,14).

As the effect of vitamin D on breast cancer is is proven we aimed to reveal vitamin D levels in women with breast cancer at the time they apply to our clinic to receive radiotherapy.

Patients And Methods

Five hundred and sixty one women with primary breast cancer who were treated in our clinic between January 2018 and December 2019 were enrolled in this study. This study was based on a retrospective analysis of vitamin D blood levels and received approval by local Ethical Committee. All patients were treated in agreement with the Helsinki declaration and provided written informed consent.

Blood samples were collected at initial presentation before the initiation of radiotherapy, after the other treatment modalities (chemotherapy and surgical therapy) were completed. Serum 25(OH) D levels were studied by the ELISA technique on the blood samples and the values were documented in ng/ml.

The median age was 55.86 years (between 20 – 78 years). All of the patients were treated with curative intend. None of the patients had metastatic disease. All of the patients were Turkish people living in Turkey. Neither foreign patients nor Turkish people living outside Turkey were included in the study. All of the patients were given chemotherapy either neadjuvant or adjuvant setting. Surgical treatment was performed to all patients as either radical or breast conserving mastectomy. None of the patients had syncronic or metacronic second malignancy. No pregnant patient was included in the study. Having bilaterally breast cancer was a cause to be dismissed from the study.

Statistical analyzes were done by PASW statistics SPSS 17.

Results

The median 25(OH)D level was 11.92ng/ml (between 1.13 ng/ml and 63.78 ng/ml) and the mean 25(OH)D level was 13.91ng/ml (SD 9.7). The levels of 25(OH)D are summarised in table 1.

Deficiency was detected in 456 patients (81.28%) and insufficiency was detected in 61 patients (10.87%). (Table 2)

The frequency of vitamin D levels are shown in figure 1.

No statistically significant correlation between age and 25(OH)D levels was detected (p=0.61) (Figure 2)

Discussion

In a study from Turkey vitamin D deficiency or insufficiency was detected as high as 88.4% (15). In another Turkish study, in 50% of women, vitamin D levels were also low (8). As we conducted our study to reveal the vitamin D levels in women with breast cancer, no data about men was collected. Hofmann JN et al collected blood samples at 3 time points over a 5 year period to evaluate within-person variability and reached the conclusion that serum 25(OH)D concentration at a single point in time may be a useful biomarker of vitamin D status (16). We, in our study, collected blood samples at a single point in time and used blood 25(OH)D concentration to evaluate vitamin D status. Vitamin D deficiency or insufficiency was seen regardless of the seasons or months and our patients were all over Turkey. We have found that regardless of the

Table 1. Distribution of 25(OH)D levels

25(OH)D level	# of patients	% of patients
<10 ng/ml	247	44.02
10 -19ng/ml	209	37.25
20-29ng/ml	61	10.89
30-39ng/ml	29	5.17
40-49ng/ml	9	1.60
50-59ng/ml	3	0.53
60-69ng/ml	3	0.53

Table 2. Vitamin D deficiency and unsufficiency distrubition

	# of patients	% of patients
Deficiency(serum 25OHD below 20 ng/ml)	456	81.28
Insufficiency (serum 25OHD between 20-30 ng/ml)	61	10.87
Total	517	92.15

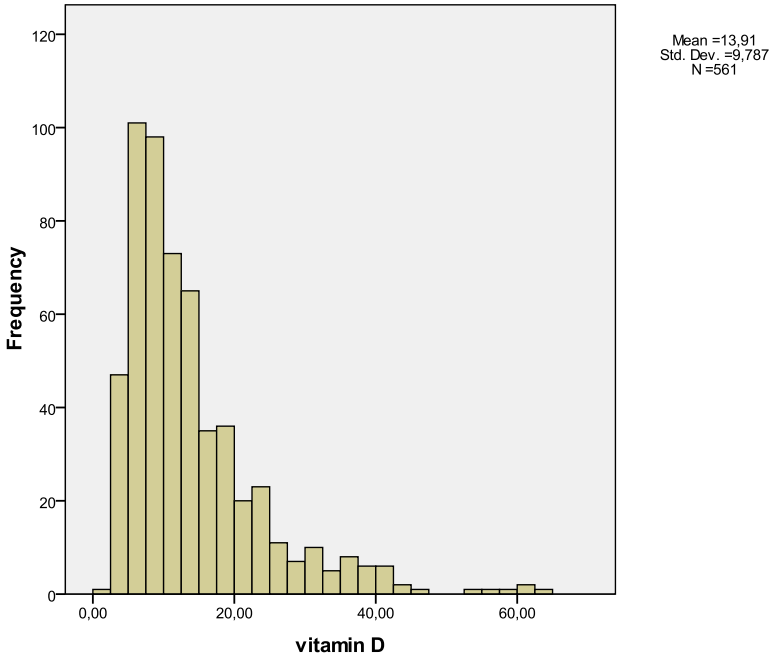

Figure 1. The frequency of vitamin D levels

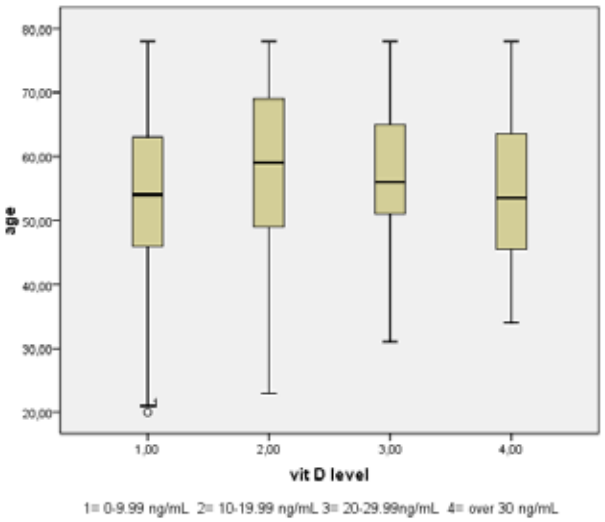

Figure 2. Age and vitamin D level correlations

factors there was either defficiency or insufficiency. As mentioned in Kennel's study (1), we thought that this may be due to patients staying indoor and protecting themselves from UVB during their cancer treatments (either chemotherapy or operation).

Shamsi et al categorised 25(OH)D levels to four groups; as severely deficient (< 12 ng/ml), deficient (12 -1 9 ng/ml), insufficient (20 -30 ng/ml) and sufficient (> 30 ng/ml). They have found that 60.2% of women had 25(OH)D levels < 20 ng/ml and 38.4% of women had 25(OH)D levels < 12 ng/ml. (10). We have taken levels below 20 ng/ml as deficiency and between 20-30 ng/ml as insufficiency and found that 517 of 561 patients (92.15%) had low levels of vitamin D.

In a study with 374 breast cancer patients it was figured out that having cancer can make negative changes in vitamin D levels (9,17). In our study changes after radiotherapy is unknown because in all patients with deficiency or inadequacy, replacement was performed.

In Mendelian Randomization studies alles were studied to predict concentrations of vitamin D (9, 18). In different MR analysis different result were reached; some came to conclusion that no correlation between vitamin D concentration and cancer incidence or mortality (20) where some supported the connection between vitamin D levels and cancer (18-20). The reason for different results may be due to the usage of population mean concentrations (9). In our study, we did not use Mendelian Randomization, but either the deficiency or inadequacy rates were high in Turkish women which in fact plays role in prognosis in breast cancer (9). Also, at the end of the Mendelian study it was concluded that further studies are needed to distinguish the effects of vitamin D.

There was no correlation between age and vitamin D levels in our study and also,Vurgun et al found that neither the age nor the race has got effect on vitamin D levels, which was shown in some other similar studies (13, 21).

In a meta-analysis of 40 articles with 111582 patients from Turkey, prevalence of vitamin D deficiency was found to be as high as 63% for general population and 64.7% for young women (22). Also around Izmir region (Agean coast of Turkey) vitamin D levels were reported low in over 90% of participants. Although

our hospital where this study was done, is located in Ankara, the treatment is provided for patients from almost all over Turkey. The results of this meta-analysis and the study point out that vitamin D levels in Turkish people should be measured periodically and to be corrected whenever diagnosed (23).

While cancer patients who have got malnutrition and/or malabsorbtion are under risk (1) we even found that breast cancer patients without evident malnutrition can have low vitamin D levels. Also there was no impaired oral intake and/or intestinal absorbtion in our patients. Vitamin D storage status can be accuratly evaluated by blood 25(OH)D levels (1). We, in our study also analysed 25(OH) D levels to asses vitamin D deficiency.

This study points out that vitamin D levels in breast cancer patients people should be measured and be corrected whenever diagnosed. It must be kept in mind that adequate vitamin D intake can not be obtained via a sole way like only UVB exposure or only oral intake. Supplementation of vitamin D is easy and not expensive. The most important part of the treatment is to think about deficiency because it is often underdiagnosed.

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Correspondence:
F. İlknur Kayalı
Adress: Ankara City Hospital Radiation Oncology Dept. Bilkent, Ankara, Turkey
e-mail: ilknurkayali@yahoo.com
phone: 0 539 844 75 58