RESEARCH ARTICLE

Vitamin D Levels in Patients with Breast Cancer: Importance of Dressing Style

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Abstract

Background: Vitamin D deficiency is a potentially modifiable risk factor that may be targeted for breast cancer (BC) prevention. It may also be related to prognosis after diagnosis and treatment. The aim of our study was to determine the prevalence of vitamin D deficiency as measured by serum 25-hydroxy vitamin D (25-OHD) levels in patients with BC and to evaluate its correlations with life-style and treatments. Materials and Methods: This study included 186 patients with stage 0-III BC treated in our breast center between 2010-2013. The correlation between serum baseline 25-OHD levels and supplement usage, age, menopausal status, diabetes mellitus, usage of bisphosphonates, body-mass index (BMI), season, dressing style, administration of systemic treatments and radiotherapy were investigated. The distribution of serum 25-OHD levels was categorized as deficient (<10ng/ml), insufficient (10-24 ng/ml), and sufficient (25-80 ng/ml). Results: The median age of the patients was 51 years (range: 27-79 years) and 70% of them had deficient/insufficient 25-OHD levels. On univariate analysis, vitamin D deficiency/insufficiency was more common in patients with none or low dose vitamin D supplementation at the baseline, high BMI (≥25), no bisphosphonate usage, and a conservative dressing style. On multivariate analysis, none or low dose vitamin D supplementation, and decreased sun-exposure due to a conservative dressing style were found as independent factors increasing risk of vitamin D deficiency/insufficiency 28.7 (p=0.002) and 13.4 (p=0.003) fold, respectively. Conclusions: The prevalence of serum 25-OHD deficiency/insufficiency is high in our BC survivors. Vitamin D status should be routinely evaluated for all women, especially those with a conservative dressing style, as part of regular preventive care, and they should take supplemental vitamin D.

Keywords: Bisphosphonate - breast cancer - chemotherapy - dressing style - radiotherapy - vitamin D - Turkey

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Introduction

Vitamin D is a fat soluble vitamin that regulates important number of body functions including calcium absorbtion, bone metabolism, neuromuscular function and immunity. Modest amount of circulating levels of 25-OHD is gained from dietary sources and the majority of vitamin D is produced naturally in the skin by the solar ultraviolet B radiation. In some places with limited sunlight for much of the year, such as northern Europe, it is difficult to maintain an optimal vitamin D level through diet alone. However, even in some of the sunniest areas of the World, rickets in children is a major health problem because wearing clothes that cover the whole body. As many as 35-80% of children in Saudi Arabia, India, Turkey, Israel, and Egypt are vitamin D deficient (Holick, 2006). Similar to that of children, vitamin D deficiency in women is also usual in some countries since they completely cover their bodies.

Preclinical studies support various antitumor effects of vitamin D in breast cancer (BC) such as inhibition of cell proliferation, induction of cell differentiation, promotion of apoptosis, decreasing inflammation with downregulation of cyclooxygenase-2, decreasing of angiogenesis, inhibition of estrogen pathway and also inhibition of invasion and metastasis (Colston et al., 1989; Mantell et al., 2000; Nagpal et al., 2005; Shao et al., 2012). Due to the increasing concern of the role of vitamin D in the development and prognosis of the BC, based on a Pubmed search between 1990-November 2008,

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the total number of articles related to BC and vitamin D have increased almost six-fold (Goodwin, 2009).

Bone health stays another particular concern for BC survivors because of the higher fracture risk than the normal population (Chen et al., 2005). Ecological studies have proven that decreased sunlight exposure increases the BC incidence and mortality (Gorham et al., 1990; Garland et al., 1990; Grant, 2002). A 4-year, population-based, double-blind, randomized placebo-controlled trial has shown that improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women (Lappe et al., 2007). In addition to preventional role of vitamin D in BC development, various studies and a large cohort study investigating the association between vitamin D and BC survival have shown that women with vitamin D deficiency had a worse outcome (Robsahm et al., 2004; Porojnicu et al., 2007; Goodwin et al., 2009; Hatse et al., 2012). Additionally, it has been reported that 25-OHD levels were significantly lower in patients with locally advanced or metastatic BC patients (Palmieri et al., 2006). It has been also demonstrated that vitamin D compounds potentiate apoptosis induced by adriamycin, paclitaxel, radiation, and tamoxifen (Sundaram and Gewirtz, 1999; Sundaram et al., 2000; Wang et al., 2000). These findings indicate that maintenance of adequate vitamin D concentrations during adjuvant treatment may enhance the effects of such treatment and prolong survival.

Present study was undertaken to determine the prevalence of vitamin D deficiency with the measurement of serum 25-hydroxyvitamin D (25-OHD) levels in BC patients and to evaluate the correlation of vitamin D deficiency with patient and treatment related factors.

Materials and Methods

Study population

The study was conducted in Istanbul, a cosmopolitan city of Turkey, located at 41° N 29° E. Between 2010 and 2013, the electronic data of breast cancer was screened and a total of 186 women with BC who had measured serum 25-OHD levels were included in the study. Patients with any other cancer history were excluded. Patient demographics and treatment characteristics are summarized in Table 1. A total of 164 (88.2%) patients underwent breast conserving surgery, 22 (11.8%) had modified radical mastectomy. There were 11 (5.9%), 79 (42.5%), 61 (32.8%) and 35 (18.8%) patients with pathologic stage 0, I, II, and III BC respectively. All of the patients received postoperative radiotherapy (RT), 113 (60.8%) patients received adjuvant chemotherapy (CT). Among all CT regimens included anthracyclines ± taxanes. For 31 (16.7%) patients, trastuzumab therapy was planned for one year period. A total of 29 among 74 (% 39.8) premenopausal patients received LHRH agonist and tamoxifen. Twenty two (11.8%) patients were using bisphosphonates with the diagnosis of osteopenia or osteoporosis. The first determination of 25-OHD levels was calculated median 8.5 months (range:1-104 months) after CT administration and median 7 months (range:0-132 months) after RT administration. The year was divided into two seasons as winter (October-March) and summer (April-September) months. Thirty-eight (20.4%) of the patients had conservative dressing style covering whole body with a scarf. According to the body-mass index (BMI) 126 (67.7%) cases were overweight or obese (BMI≥25). A total of 113 (60.8%) patients had bone-mineral densitometry (BMD) records before or after the baseline 25-OHD determination.

During the baseline calculation of 25-OHD level, 173 (93%) of the patients were using none or oral daily 400-1000 IU vitamin D supplementation and 13 (7%) of them were using high dose (100000-300000 IU/ month) supplementation. Patients were divided into two categories according to daily low dose vs. high dose supplementation groups after 25-OHD determination and effectiveness of various supplementation types on vitamin D levels were also investigated. Based on retrospective data collection, 30 patients received daily low dose (400-1000 IU) and 80 patients received high dose (100000-300000 IU/ month) supplementation for three months. 25-OHD levels were reassessed in the following 12-16 weeks in 110 of the patients. The distribution of serum 25-OHD levels was categorized as deficient (<10 ng/ml), insufficient (10-24 ng/ml), and sufficient (25-80 ng/ml).

The correlation between serum baseline 25-OHD levels and the supplementation type, age, menopausal status, diabetes mellitus (DM), usage of bisphosphonates, BMI, season, systemic treatments, RT and dressing style were investigated. The relation with vitamin D levels and BMD results were also studied. BMD was measured by dual energy X-ray absorptiometry using a Lunar densitometer made by General Electric. BMD was determined lumbar spine and total hip with in accordance to the International Society of Clinical Densitometry (Hans et al., 2006). Patients with BMD records were divided into 3 groups according to T scores as normal (0 to -1) (n=36), osteopenic (-1 to-2.5) (n=60) and osteoporotic (≤-2.5) (n=21).

Determination of serum 25-OHD levels

Serum samples were collected after an overnight fast of at least 12 hours, spun, and analyzed immediately in a single laboratory. Total 25-OHD (vitamin D2 ergocalciferol and D3 cholecalciferol) was measured by direct electrochemiluminescence immunoassay (Roche Diagnostics GmbH, D-68298 Mannheim, Germany) on a Roche Modular E 170 analyzer. It is a competitive immunoassay in which the binding protein of vitamin D is inactivated during incubation.

Statistical analysis

Data analysis was done by using SPSS version 15. Relation of vitamin D deficiency/insufficiency with age, menopausal status, stage, season, dressing style, type of initial vitamin D supplementation, CT/RT administration, HT, trastuzumab, bisphosphonate use and DM were determined by using the Chi-square tests. Multivariable linear regression models were used to study the association between 25-OHD levels and patient, tumor and treatment characteristics. A p value of≤0.05 was considered statistically significant. For continuous variables, the Mann-Whitney U test was used for comparisons between groups according to dressing code and different supplementation types. Friedman test was used for comparisons between baseline and supplemented 25-OHD levels. BMD status and 25-OHD levels were investigated with Mann-Whitney U test.

Results

The median age of the patients was 51 years (range: 27-79 years) and median level of baseline 25-OHD was 19.76 ng/ml (range: 2.5-67.43 ng/ml) in all cohort. According to baseline calculation; 25% and 45% patients had deficient and insufficient 25-OHD levels, respectively. Median 25-OHD levels were significantly lower in patients with conservative dressing style [8.51 ng/ml (range: 2.5-40 ng/ml) *vs* 21.24 ng/ml (3.13-67.43ng/ml) p<0.001, z= -5.916].

On univariate analysis, vitamin D deficiency/insufficiency was more common in patients with none or low dose vitamin D supplementation at the baseline, high BMI (≥25), no bisphosphonate usage, and the conservative dressing style (Table 1). Among all patients, BMD records were obtained for 113 (60.8%) patients. Of these 113 patients, only 34 (20.4%) patients had normal BMD. Remaining 58 (51.3%) had osteopenic and 21 (18.6%) patients had osteoporotic findings. Serum 25-OHD level was found lowest in osteoporotic group (n=21) and 62% of whom were using bisphosphonates. In contrast, more patients had low vitamin D levels in osteopenic group (n=58) and 12% of them were on bisphosphonates. In our study, we did not show an inverse association between the 25-OHD levels and CT, RT, HT and trastuzumab use.

On multivariate analysis, none or low dose vitamin D supplementation at the baseline, and decreased sunlight-exposure due to conservative dressing style were found as independent factors increasing risks of vitamin D deficiency/insufficiency 28.7 (p=0.002) and 13.4 (p=0.003) fold, respectively (Table 2).

Among all patients, 110 of them had reassessment of 25-OHD levels 12-16 weeks after supplementation. High dose supplementation group (n=80) significantly increased 25-OHD levels [from median 13.87 ng/ml

Table 1. Univariate Analysis of Clinical Parameters and Treatment Characteristics

		Vitamin D deficient/insufficient		Vitamin D normal		Total		
		n	%	n	%	n	%	p
Age (years)	≤50	63	48.5	25	44.6	88	47.3	0.632
	>50	67	51.5	31	55.4	98	52.7	
Stage	0-IIA	88	67.7	40	71.4	128	68.8	0.740
	IIB-IIIC	42	32.3	16	28.6	58	31.2	
Menopausal status	Premenopausal	51	39.2	23	41.1	74	39.8	0.943
	Postmenopausal	79	60.8	33	58.9	112	60.2	
Season	October-March	82	63.1	29	51.8	111	59.7	0.150
	April-September	48	36.9	27	48.2	75	40.3	
Dressing style	Modern	94	72.3	54	96.4	148	79.6	<0.001*
	Conservative	36	27.7	2	3.6	38	20.4	
Initial vitamin D supplementation								
	None or 400-1000 IU/day	129	99.2	44	78.6	173	93	<0.001*
	100.000-300.000 IU/month	1	0.8	12	21.4	13	7	
Radiotherapy	≤7 months	70	53.8	26	46.4	96	51.6	0.353
	>7 months	60	46.2	30	53.6	90	48.4	
Hormonotherapy	No	24	18.5	10	17.8	34	18.3	0.687
	Tamoxifen	61	46.9	23	41.1	84	45.2	
	Aromatase Inhibitor	45	34.6	23	41.1	68	36.6	
Chemotherapy	Yes	83	63.8	30	53.6	113	60.8	0.188
	No	47	36.2	26	46.4	73	39.2	
Trastuzumab	Yes	22	16.9	9	16.1	31	16.7	1.000
	No	108	83.1	47	83.9	155	83.3	
Diabetes mellitus	Yes	21	16.2	6	10.7	27	14.5	0.460
	No	109	83.8	50	89.3	159	85.5	
BMI (kg/m^2)	≤25	36	27.7	24	42.9	60	32.3	0.042**
	>25	94	72.3	32	57.1	126	67.7	
Bisphosphonates	Yes	9	6.9	13	23.2	22	11.8	0.004*
	No	121	93.1	43	76.8	164	88.2	

*=p<0.01,**=p<0.05 (Pearson Chi-Square, Continuity Correction, Fisher's Exact Tests)

Table 2. Factors Effecting Low Levels of 25-OHD in Breast Cancer Patients

	Factors	B	SH.	Wald	df	p	Exp(B)	%95 CI
Model-3	Initial vitamin D intake(No or low dose)	3.357	1.096	9.377	1	0.002	28.709	3.348-246.163
	Bisphosphonate usage (No)	1.234	0.545	5.125	1	0.024	3.436	1.180-10.003
	Dressing style (conservative)	2.596	0.882	8.662	1	0.003	13.404	2.380-75.493
	Stable value	0.074	0.642	0.013	1	0.908	1.077	

Method=Forward Stepwise (Likelihood Ratio); Dependent variable: vitamin D deficiency/insufficiency (1=yes; 0=no); R^2=0.217

(range: 2.5-51.29 ng/ml) to 38.48 ng/ml (range: 22-75ng/ml)] compared with low dose supplementation group (n=30) [from median 18.56 ng/ml (4-47.91ng/ml) to 19.75ng/ml (7.22-34.22 ng/ml)] ($p<0.001$, $z=-9.296$). Half of the patients in the low dose vitamin D supplementation group had decreased 25-OHD levels. All patients tolerated high dose supplementation very well and none of the patients had toxic levels of 25-OHD after high dose supplementation for three months.

Discussion

To our knowledge, the present study is the first study from the Turkey to date surveyed the large cohort of heterogeneous women with BC for vitamin D deficiency. Our study suggests that 25-OHD levels were deficient/insufficient in 70% of BC patients despite the sunny climate in our region. Dressing style and supplementation type were found as major determinants for circulating vitamin D levels. Life-style including; ethnic and religious variations of dressing style, eating habits which effects dietary intake and outdoor activity status also play important role of serum vitamin D levels. Previous studies have linked low levels of vitamin D with conservative dressing style even in a sunny climate like in Middle-East (Holick, 2007). Other studies from Turkey have shown vitamin D deficiency in pregnant women and adolescent girls especially those who follow a religious dress code (Hatun et al., 2005; Halicioglu et al., 2012). In a Lebanese study postmenopausal osteoporotic Muslim and Christian women were compared for differences in 25-OHD levels. In a multivariate analysis in Muslims, inadequate vitamin D supplementation and the dress code covering the arms were independent predictors of 25-OHD inadequacy ($p<0.001$ for both variables) (Gannage-Yared et al., 2009). Finally, interaction tests comparing the results for Christian and Muslim women revealed that BMI ($p=0.045$) and the exposure of arms to sunlight ($p=0.012$) were significant variables.

A recent study from United States reported that 75.6% of American patients with BC had low levels of vitamin D (Neuhouser et al., 2008). The main factors contributing to the cutaneous production of vitamin D are season, latitude and the day-time length, clothing-style and sunscreen pigmentation of the skin and ageing. Seasonal variations are also important, this is supported by clinical studies that show a peak of the 25-OHD levels in late summer/autumn (Moan et al., 2005). Skin pigmentation has an important role of Vitamin D synthesis; in Crew et al's (2009) study after one year of vitamin D supplementation (400 IU), less than 15% of the white and Hispanic women and none of the black women achieved sufficient (≥30ng/ml) levels in the serum. Daily low-dose vitamin D supplementation also failed to significantly increase 25-OHD levels in BC patients with insufficient (<32ng/ml) vitamine D levels at baseline in the retrospective study by Peppone et al. (2011) which was similar to our results. Present study suggests that, both baseline and following supplementation with high dose vitamin D, 25-OHD levels are significantly higher compared to low dose vitamin D intake ($p<0.001$) and well tolerated without uncontrollable toxic levels. Similarly, in the study by Khan et al. (2010), weekly high doses vitamin D supplementation in women using letrozole for BC treatment was tolerated very well and decreased the incidence of musculoskeletal symptoms. A recent review found no reports of toxicity in patients taking <20.000 IU per day of vitamin D or in those with a serum 25-OHD concentration <200ng/ml during an extended period (Hathcock et al., 2007). Efficacy and safety of high dose vitamin D supplementation should be tested in well designed randomised studies and guidelines are needed for optimal vitamin D supplementation. In our study, calcium and vitamin D supplementation was recommended in patients receiving bisphosponates, and majority of the patients (59%) who were on bisphosphonates also received initially high dose supplementation. Vitamin D deficieny/insufficieny was found lowest in the osteoporotic group (n=21) because 62% of the patients were using bisphosphonates. In contrast, more patients had low vitamin D levels in osteopenic group (n=58) because only 12% of them were on bisphosphonates. Therefore no bisphosphonate usage was found as an independent factor increasing risk of vitamin D deficiency/insufficiency 3.4 fold ($p=0.024$) (Table 2).

Treatment related factors effecting vitamin D levels should also be investigated. Side effects of CT such as loss of appetite and nausea effecting the change of eating habits and absorbtion of vitamin D from intestines, may cause vitamin D deficiency or insufficiency. It may also decrease the physical activity and increase of BMI in terms of adipose tissue. Patients receiving RT usually decrease their outdoor activities and this may reduce sunlight exposure. A study by Jacot and colleagues (2012) have shown that at baseline, 79.5% of patients had lower than 30ng/ml vitamin D levels, increasing to 97.4% at the end of the neoadjuvant CT ($p<0.0001$), and severe insufficiency also increasing from 10.4% to 23.4% of cases. In Goodwin et al 's (2009) study in early BC patients who received adjuvant CT had lower vitamin D levels than those who did not ($p=0.02$). In another study, adjuvant CT has been found to reduce plasma vitamin D concentration significantly, but the study size (n=20) was small (Santini et al., 2010). Other studies (Crew et al., 2009; Peppone et al., 2011) and our study have shown no relation between the CT and the low levels of vitamin D. Radiotherapy correlated significantly lower baseline 25-OHD levels in Peppone et al's (2011) study ($p=0.01$); however, we did not find any correlation. In our study, first determination of 25-OHD levels were conducted median 8.5 months (range: 1-104 months) after CT administration and median 7 months (range: 0-132 months) after RT administration. Timing with CT/RT administration and determination of baseline vitamin D levels were not given by Peppone et al (2011), and their study had retrospective data collected during a 4-years period. This heterogenous group may mask the results for relation with CT/RT. Their data suggests that suboptimal vitamin D levels were more common in women with advanced stage disease, non Caucasians and those who received RT. Stage is not found as a significant factor for low vitamin D levels in our study, despite the other trial results (Palmieri, 2006 ; Khan, 2010). Lastly, the inhomogeneity of the duration between the systemic treatment and the measuring time of 25-OHD levels may play a role in showing no association between vitamine D deficiency/insufficiency and adjuvant CT in our study. As in line with Vrieling et al's study (2011), we did not find clear differences in RT or HT use versus low levels of 25-OHD. Various studies have also shown that obesity and lower physical activity are associated with low serum levels of vitamin D in patients with BC (Lagunova et al., 2010; Vrieling et al., 2011; Friedman et al., 2012). In our study, according to the univariate analysis BMI>25 was found significantly associated with low levels of vitamin D levels, however correlation was not significant in multivariate analysis.

The major limitation of our study was its' retrospective usage of electronic data of our hospital and the nonuniform periods between the calculation of baseline 25-OHD level and CT/RT administration. As all measurements were done in the last 3 years we did not investigate any correlation between the suboptimal levels of vitamin D and BC outcome. Daily diet, socioeconomic and educational status, daily physical activity were not recorded and therefore were not studied by us. Nevertheless, the strength of our data is that, it includes a relatively large heterogenous sample of BC patients uniformly treated with adjuvant systemic therapy and RT from a single BC center and all measurements being done in a single laboratory.

In light of current data, suboptimal vitamin D level is very common in the community and in BC patients. Cancer treatments may further decrease vitamin D level by causing side effects that result in malnutrition, and change in life style and in eating habits as an indirect effect. Sunlight exposure and vitamin D supplementation seem the most important two parameters in both pre- and posttreatment periods. The results of treatments may aggravate the deficiency/insufficiency of vitamin D levels but we could not show that these factors are independent variables.

In conclusion, in our patients high frequency of vitamin D deficiency was found during and after the treatment. Dietary and supplemental vitamin D intake and sun exposure are modifiable factors. The oncologists should be aware of vitamin D deficiency in BC patients and must educate patients about their life-style and habits. Vitamin D status should be routinely evaluated for all women especially patients with conservative dressing style as part of regular preventive care. They should take supplementation if they have vitamin D deficiency/insufficiency and should be encouraged to expose to sunlight. Controlled high dose supplementation seems more effective to achieve high levels of vitamin D levels in a short period of time.

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