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THE EFFECT OF VITAMIN D LEVELS ON BREAST CANCER-RELATED LYMPHEDEMA

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ABSTRACT

The purpose of this study was to compare plasma vitamin D levels in patients with breast cancer-related lymphedema (BCRL), breast cancer (BC) without lymphedema, and healthy populations, as well as relationship between clinical variables, lymphedema severity grading, and circulating vitamin D concentrations. This Case-control study was conducted between June 2017 and January 2025. The study comprised three cohorts: a case cohort of individuals diagnosed with breast cancer-related lymphedema (BCRL), a disease-matched control cohort of breast cancer (BC) patients without lymphedema (demographically aligned with the BCRL cohort by age and sex), and a reference cohort of healthy participants matched by age and sex. A total of 603 female individuals were included in the study with 201 individuals in each group. Post-hoc Games-Howell test analyses revealed a lower level of Vitamin D in the BCRL group compared to the BC and control groups (p<0.001, p<0.001) and lower levels in the BC group compared to the control group (p<0.001). Vitamin D deficiency was statistically significantly more frequent in BCRL group than in BC and control groups (p:<0.001) and the proportion of those with normal vitamin D were statistically significantly more frequent in control group than in BCRL and BC and control groups (p:<0.001). Analysis revealed a strong, significant negative correlation between circulating vitamin D concentrations and advancing lymphedema stage (r: -0.578, p:<0.001). These observations imply that hypovitaminosis D may contribute to breast cancer pathogenesis and modulate the risk of treatment-associated morbidities, particularly lymphedema progression. Therefore, it is recommended that individuals diagnosed with BC or at risk of lymphedema have their vitamin D levels checked regularly and take supplements if necessary.

Keywords: Breast Cancer-Related Lymphedema, Breast Cancer, Vitamin D, Vitamin D Deficiency, Vitamin D Insufficiency

INTRODUCTION

Globally, breast cancer (BC) is the second most frequently diagnosed malignancy and persists as the predominant cancer in women (1). A frequent complication of BC therapy is breast cancer-related lymphedema (BCRL), a chronic condition arising from impaired lymphatic drainage (2). This insufficiency triggers a cascade of inflammatory responses culminating in symptoms such as localized discomfort and heightened susceptibility to infections. Individuals with BCRL in the ipsilateral upper limb often report edema, sensations of heaviness, pain, paresthesia, re-

duced flexibility, and diminished motor function, including compromised grip strength and coordination. The condition is associated with physical deformities, restricted joint mobility, and significant disruptions to routine tasks, self-care, occupational productivity, and interpersonal engagements. Furthermore, BCRL frequently exacerbates socioeconomic challenges due to increased healthcare costs and reduced work capacity (3). Epidemiological studies indicate a higher prevalence of lymphedema in women, individuals in middle to later adulthood, and those with elevated body mass indices (4).

Vitamin D serves a critical physiological function in preserving skeletal integrity and musculoskeletal health. Its metabolically active metabolite, 1,25-dihydroxyvitamin D3 (calcitriol), acts as the primary hormonally active form, orchestrating systemic calcium and phosphate homeostasis to sustain fundamental cellular processes and promote proper bone mineralization. Hypovitaminosis D demonstrates a high global prevalence, with epidemiological studies indicating its widespread occurrence across diverse populations (5). Documented determinants encompass chronological age, elevated body mass index (BMI), habitual sunscreen application, limited ultraviolet (UV) exposure due to restricted outdoor activity, melanin concentration, and residence at higher latitudes (6). Recent years have witnessed a marked expansion in scientific inquiry examining the non-skeletal physiological roles of vitamin D. Vitamin D insufficiency has been implicated in heightened susceptibility to diverse pathologies, including metabolic disorders (e.g., diabetes mellitus, adiposity-related complications), cardiovascular pathologies, immune dysfunction and susceptibility to infections, respiratory conditions such as asthma, chronic gastrointestinal inflammation (e.g., inflammatory bowel disease), neurodegenerative conditions, and malignan-cies (7, 8).

Various precautions are recommended for cancer patients with lymphedema or those at risk of developing lymphedema. Some of these include applying sunscreen and avoiding being outdoors during maximal sun intensity. Clinical management protocols, compounded by psychosocial distress and mobility restrictions that limit ultraviolet (UV) light exposure, may also contribute to suboptimal vitamin D synthesis in individuals with lymphedema (9). Research into hypovitaminosis D has identified associations with breast cancer susceptibility and disease progression, with evidence suggesting its role in elevating post-treatment morbidity risks such as lymphedema development (10). The relationship between serum 25-hydroxyvitamin D concentration and health outcomes in BC survivors was examined in a systematic review in 2016 and findings indicate that vitamin D deficiency may be associated with complications such as lymphedema (11). A 2019 Turkish cohort analysis demonstrated significantly reduced circulating 25(OH)D levels in individuals with lymphedema relative to healthy controls, with a severity-dependent decline observed in Stage III patients exhibiting markedly lower concentrations compared to their Stage I counterparts (12). A 2020 Turkish case-control investigation reported no significant intergroup disparity in serum 25(OH)D levels between breast cancer cohorts with and without lymphedema. Furthermore, within the lymphedema cohort, circulating 25(OH)D concentrations showed no significant associations with patient-reported outcomes (VAS, Q-DASH scores) or objective metrics of limb asymmetry, including circumferential and volumetric measurements (13).

The association between BCRL and vitamin D is based on the anti-inflammatory and immunomodulatory effects of vitamin D. However, studies directly examining this association are limited. Current studies suggest that vitamin D deficiency may increase the risk of lymphedema and that vitamin D supplementation may help alleviate symptoms. This study aimed to compare plasma vitamin D levels in patients with breast cancer-related lymphedema (BCRL), breast cancer (BC) without lymphedema, and healthy populations, as well as relationship between clinical variables, lymphedema severity grading, and circulating vitamin D concentrations.

PATIENTS AND METHODS

Study Design

This Case-control study was conducted in the Physical Medicine and Rehabilitation Clinic between June 2018 and September 2024. The study protocol was approved by Yozgat Bozok University Non-invasive Clinical Research Ethics Committee (2024-GOKAEK-2415_2024.12.18_247). All procedures performed in studies involving human were in accordance with the ethical standards of the institutional research committee (Yozgat Bozok University Non-invasive Clinical Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patients

Patients between the ages of 18-65 diagnosed with lymphedema associated with BCRL and who were studied with vitamin D were included as the patient group; patients between the ages of 18-65 who were diagnosed with BC, and were studied with vitamin D, and were of similar age and gender to the patient group but did not have lymphedema were included as the patient control group; healthy individuals between the ages of 18-65 who were studied with vitamin D, and were of similar age and gender to the patient group were included as the control group. We included patients in the study whose Vitamin D was studied in June, July and August in all three groups since serum 25-hydroxyvitamin D concentration is affected by seasonal changes.

Cancer patients with or without lymphedema are followed up at Oncology outpatient clinics at certain periods and many patients' Vitamin D, Calcium, Phosphorus, Creatinine results are checked. The majority of lymphedema patients were over the age of 50 and most of the patients have additional diseases; they were followed up at Internal Medicine outpatient clinics and many patients' Vitamin D, Calcium, Phosphorus, Creatinine and Parathyroid Hormone results are checked. The majority of lymphedema patients are over 50 years old and since osteoporosis develops due to both menopause and the steroid and chemotherapy drugs applied, patients were examined in Physical Medicine and Rehabilitation, Oncology and Internal Medicine outpatient clinics for bone densitometry and vitamin D, calcium, phosphorus, creatinine and Parathyroid Hormone results. For these reasons, the majority of lymphedema patients apply to Oncology, Internal Medicine, Endocrinology and Physical Medicine and Rehabilitation outpatient clinics at certain intervals, and mostly the patients' vitamin D, calcium, phosphorus, creatinine and Parathyroid Hormone results are available in the system. We were able to access the patients' blood results from these data. Patients whose relevant tests cannot be accessed were excluded from the study. Healthy individuals between the ages of 18-65 are routinely asked to undergo routine complete blood and biochemistry tests at our hospital's Check-Up Clinic; We were able to Access the results of healthy controls from these data.

Key demographic variables of the participants, such as chronological age and gender identity, additional diseases, which extremity had lymphedema, whether or not they had undergone surgery due to cancer, time elapsed after the operation, whether or not they had received chemotherapy and radiotherapy, if previously studied retrospectively, Doppler ultrasound and lymphoscintigraphy results, duration of lymphedema, stage of lymphedema, Vitamin D, Calcium, Phosphorus, Creatinine and Parathyroid hormone results were recorded by retrospectively scanning through the statistics module (HBYS-Hospital Information Management System data statistics module).

Statistical analysis

Categorical variables were analyzed using Pearson chi-square and Fischer's exact probability test according to the expected frequency for between-group differences. The analysis of the difference between groups for continuous variables was compared using Student T test and One-Way Analysis of

TABLE 1
Demographic and Clinical Features of Patients in each Group

	BCRL group (n=201)	Breast cancer group (n=201)	Control group (n=201)	p
Age (Mean± SD)	53.50±11.45	54.92±7.53	53.32±10.27	0.135 [a]
Gender - women (n/%)	201(100)	201(100)	201(100)	
Direction of affected limb (n/%)- Right-sided	68(33.8)	-	-	
Left-sided	133(66.2)	-	-	
Comorbid diseases (n/%)				
None	78 (38.8)	70 (34.8)	-	0.736[b]
HT	93 (46.3)	89 (44.3)	-	0.731[b]
DM	63(31.4)	65(32.4)	-	0.132[b]
Hypothyroidis	7(3.5)	5(2.5)	-	
m CAD	6 (3.0)	10 (5.0)	-	
Asthma	6 (3.0)	10 (5.0)	-	
Other	3 (1.5)	6 (3)	-	
Time after surgery (months) (Mean± SD)	44±22.8	41±23.8	-	0.531[c]
Chemotherapy history(n/%)	199(99)	199(99)	-	0.688[b]
Radiotherapy history (n/%)	180(89.6)	167(83.1)	-	0.040 [b]
Doppler USG findings (n/%) Not performed	88 (39.5)	-	-	
Normal	93 (46.3)	-	-	
Venous insufficiency	16 (8)	-	-	
Deep vein thrombosis	4 (2)	-	-	
Lymphoscintigraphic evaluation(n/%)	46 (22.9)	-	-	
Duration of lymphedema (months) (Mean± SD)	18±3.60		-	
Stage of lymphedema				
1(n/%)	54 (26.9)	-	-	
2(n/%)	112 (55.7)	-	-	
3(n/%)	35 (17.4)	-	-	
Vitamin D as (n/%)				
Deficiency (<20 ng/ml)	192(95.5)	145(72.1)	89(44.3)	<0.001 [b]
Insufficiency (20-30 ng/ml)	6(3)	42(20.9)	59(29.4)	<0.001 [b]
Normal (>30 ng/ml)	3(1.5)	14(7)	53(26.4)	<0.001 [b]

BCRL: Breast cancer- related lymphedema, SD: standard deviation, n: Number, [a] One-Way Analysis of Variance (ANOVA), [b] Chi-square test, [c] Student T test, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary arterial disease, USG: Ultrasonography,

Variance (ANOVA). Post-hoc Tukey and post-hoc Games-Howell test were used to compare numerical variables of more than two groups. Pearson correlation analysis was used for correlation analysis of factors associated with Vitamin D level in BCRL group.

RESULTS

A total of 603 women individuals were included in the study. The study enrolled three cohorts: a case cohort comprising 201 individuals diagnosed with breast cancer-related

TABLE 2
Comparison of Laboratory Parameters between Groups

	BCRL group (n=201)	Breast cancer group (n=201)	Control group (n=201)	p
Vitamin D level (ng/ml) (Mean± SD)	10.48±5.36	16.27±7.63	22.70±10.72	<0.001[a**]
Calcium level (mg/dL) (Mean± SD)	9.09±0.29	9.20±0.28	9.49±0.31	<0.001[a*]
Phosphorus level (mg/dL) (Mean± SD)	3.57±0.39	3.67±0.42	3.77±0.30	<0.001[a**]
Creatinine level (mg/dL) (Mean± SD)	0.69±0.12	0.67±0.10	0.64±0.07	<0.001[a**]
Parathyroid hormone pg/mL) (Mean± SD)	51.99±15.29	49.22±14.25	37.05±15.81	<0.001[a*]

*BCRL: Breast cancer- related lymphedema, SD: standard deviation, n: Number, [a] One-Way Analysis of Variance (ANOVA), and [*]post-hoc Tukey and ** post-hoc Games-Howell test*

lymphedema (BCRL), a disease control cohort of 201 breast cancer (BC) survivors without lymphedema, and a reference control cohort of 201 age- and sex-matched healthy participants. Demographic and clinical characteristics of women individuals in BCRL, BC and control groups are given in *Table 1*. Mean age was similar in all three groups. While there was no difference between BCRL and BC groups in terms of comorbid diseases, mean years since surgery and chemotherapy history and radiotherapy history was statistically significantly higher in BCRL group (p=0.040). Vitamin D deficiency was statistically significantly more frequent in BCRL group than in BC and control groups (p<0.001); vitamin D insufficiency and the proportion of those with normal vitamin D were statistically significantly more frequent in control group than in BCRL and BC and control groups (p<0.001).

Comparison of laboratory parameters between groups is given in *Table 2*. Post-hoc Games-Howell test revealed that Vitamin D levels were lower in the BCRL group than in BC and control groups (p<0.001, p<0.001) and lower in the BC group than in the control group (p<0.001). Post-hoc Tukey test analyses revealed that Calcium levels were lower in the BCRL group than in BC and control groups (p=0.001, p<0.001) and lower in the BC group than in the control group (p<0.001). Post-hoc Games-Howell test analyses revealed that Phosphorus level was lower in the BCRL group than in BC and control groups (p=0.036, p<0.001) and lower in the BC group than in the control group (p=0.012). Post-hoc Games-Howell test analysis revealed that creatinine level was no difference in BCRL group compared to BC group (p=0.36), higher than control group (p<0.001) and higher in BC group compared to control group (p=0.001). Post-hoc Tukey test analysis revealed that Parathyroid hormone level was no different in BCRL group compared to BC group (p=0.159) and higher than control group (p<0.001) and higher in BC group compared to control group (p<0.001).

Correlation analysis of factors related to vitamin D level in BCRL group are displayed in *Table 3*. While there was no correlation between vitamin D level and age, mean years since surgery, history of chemotherapy and radiotherapy, and duration of lymphedema in BCRL group; a strong, significant negative correlation was found between vitamin D and lymphedema stage (r:-0.578, p:<0.001), a weak correlation between vitamin D and the stage of the affected limb direction (r:-0.152, p: 0.031, lower vitamin D level in left extremity involvement), and a weak correlation between vitamin D and comorbid disease (r: 0.141, p:0.045,

TABLE 3
Correlations of Factors associated with Vitamin D level in BCRL Group

		Vitamin D level
Age	r	0.70
	p	0.324 [a]
Direction of affected limb	r	-0.152*
	p	0.031 [a]
Comorbid diseases	r	0.141*
	p	0.045 [a]
Time after surgery (years)	r	0.059
	p	0.404 [a]
Chemotherapy history	r	0.041
	p	0.565 [a]
Radiotherapy history	r	0.111
	p	0.117 [a]
Duration of lymphedema	r	0.052
	p	0.460 [a]
Stage of lymphedema	r	-0.578**
	p	<0.001 [a]

BCRL: Breast cancer-related lymphedema, [a] Pearson correlation analysis *The correlation is significant at the 0.05 level (2-tailed), **The correlation is significant at the 0.01 level (2-tailed).

lower vitamin D level in HT and DM groups).

DISCUSSION

In our cohort, the mean age of patients in the BRCL and BC groups was 53.50±11.45, similar to the literature (1,14). In the BRCL group, similar to the literature, 66.2% of the patients' affected limbs were on the left side (15); in the BRCL and BC groups, the history of chemotherapy was 99%-99% (16), while the history of radiotherapy was 89.6%-83.1%, similar to the literature (17). The reason for the statistically slightly higher rate of radiotherapy in the BRCL group may be damage to the lymphatic vessels as a side effect of radiotherapy which could slow lymphatic flow and cause lymphedema (18,19). In the BRCL group, similar to the literature, the mean duration of lymphedema was 7.33±3.60 (20,21), and the lymphedema stages of the lymphedema patients were 2 (55.7%) and 3 (17.4%), similar to the literature (22).

Vitamin D has been studied more in BC than in BRCL. Ten randomized and 15 non-randomized studies examined found evaluated serum 25-hydroxyvitamin D concentration in newly diagnosed BC patients in a 2021 review; the mean serum 25-hydroxyvitamin D concentration was found to be 26.88 ng/mL in BC patients and 31.41 ng/mL in the control group; 45.28% of BC patients had serum 25-hydroxyvitamin D concentration below 20 ng/mL, while 67.44% had a starting vitamin D level below 30 ng/mL (23). Seven randomized controlled trials on the effect of vitamin D on BC risk were evaluated in a 2021 review; vitamin D was found to have no statistically significant effect on BC risk (24). The regulatory role of vitamin D on BC was examined in a review in 2021; it was reported that there was a direct negative relationship between serum 25-hydroxyvitamin D concentration and BC risk, and active vitamin D prevents cancer invasion and metastasis (25). Most randomized clinical trials in a review in 2022 showed that a signi-

ficant reduction in BC incidence with vitamin D supplementation, and recommended that active vitamin D be used in conjunction with existing cancer treatments (26). Fourteen studies on insufficient serum 25-hydroxyvitamin D concentration and 48 on vitamin D receptor polymorphisms were evaluated in a meta-analysis conducted in 2023. It was reported that low vitamin D and some vitamin D variants were associated with BC, but the results were inconsistent (27). Vitamin D receptor expression was compared in 111 BC patients after neoadjuvant chemotherapy in a study conducted in 2024 and results demonstrated that Vitamin D receptor expression was associated with prognostic factors such as cancer burden class, vascular invasion, and lymph node involvement (28). As the majority of the literature agrees, we found lower serum 25-hydroxyvitamin D concentration in our study in 201 BC patients with a mean age of 54.92 years and a mean time since surgery of 41 months compared to the control group (22.7- 16.27).

Furthermore, the current literature presents conflicting evidence regarding the role of vitamin D in lymphedema pathogenesis. While some animal studies have demonstrated beneficial effects of vitamin D supplementation on lymphedema reduction through mechanisms such as improved macrophage migration and anti-inflammatory activity, human trials remain inconclusive. Hence, additional controlled studies are needed to elucidate this complex relationship. In support of this, a recent animal study by Aksoyler et al. reported that calcitriol treatment significantly reduced lymphedema in rats, possibly by enhancing macrophage migration and promoting resolution of lymphatic inflammation (29). No other preclinical studies focusing on calcitriol in lymphedema animal models have been published in the last five years (to our knowledge), emphasizing the novelty of the present findings. This highlights a potential therapeutic mechanism of vitamin D in lymphedema.

Current evidence is limited to two primary investigations assessing the interplay between serum vitamin D status and breast cancer-related lymphedema (BCRL) pathogenesis. It was found that serum 25-hydroxyvitamin D concentration was lower in 80 lymphedema patients with an average age of 55.5±8.9 (36-81) and an average lymphedema duration of 23.5±13.8 months compared to 80 age- and gender-matched healthy controls in a study conducted in Turkey in 2019; and a significant relationship was found between serum 25-hydroxyvitamin D concentration and age, disease duration and lymphedema stage (12). Similar to this study, we found that vitamin D level was lower in the BCRL group than in BC and control groups, a significant relationship between serum 25-hydroxyvitamin D concentration and lymphedema stage; however, we did not find a relationship between serum 25-hydroxyvitamin D concentration and age or disease duration. This difference may have been due to the fact that we included patients aged 65 and under in our study and that the average disease duration in our study was lower (55.8 months – 44 months). Serum 25-hydroxyvitamin D concentration in 37 lymphedema patients with an average age of 53.13± 10.5, with an average lymphedema duration of approximately 33 months, was compared with 37 age- and gender-matched, non-lymphedema BC patients in a study conducted in Turkey in 2020; serum 25-hydroxyvitamin D concentration did not show a statistically significant difference between lymphedema BC patients and non-lymphedema BC patients, and no correlation was found between serum 25-hydroxyvitamin D concentration and visual analog scale (VAS) and Quick Disability Questionnaire for Arm, Shoulder, and Hand (Q-DASH) scales or diameter and volume differences of the extremities in the lymphedema group (13). This situation may be due to the fact that in their study, there were 16 patients with Stage 1 lymphedema, 14 patients with Stage 2 lymphedema and 7 patients with Stage 3 lymphedema in the BCRL group, whereas in our study, there were 54 patients with Stage 1 lymphedema, 112 patients with Stage 2 lymphedema and 35 patients with Stage 3 lymphedema, meaning that there were many more patients with Stage 2 lymphedema in our study. Due to the small sample size in their study, they did not analyze the relationship between

lymphedema stage and serum 25-hydroxyvitamin D concentration, therefore, we could not compare them.

It is also important to consider the role of genetic predisposition in the development of lymphedema, as only a subset of cancer or filariasis patients develop this condition. Genetic factors may influence lymphatic, venous, adipose, or dermal structures. Moreover, understanding the local tissue activity and receptor expression of vitamin D in the skin may be more relevant than systemic serum levels, given that sun exposure and serum concentrations do not always correlate with tissue effects. Relevant studies have shown that vitamin D influences immune modulation and adipose tissue inflammation, which are integral to lymphedema development (30,31). In particular, vitamin D has been shown to modulate macrophage polarization, suppress proinflammatory cytokines like IL-6 and IL-17, and promote anti-inflammatory cytokines such as IL-10 contributing to reduced chronic inflammation according to recent immunological reviews (32). These mechanisms may help explain the variable clinical expression of lymphedema in patients with similar treatment backgrounds.

LIMITATIONS

The limitations of the study were that it was retrospective and extremity volume measurements were not evaluated.

CONCLUSION

We found lower serum 25-hydroxyvitamin D concentration in the BCRL group compared to the BC and control groups, and a strong, significant negative correlation between vitamin D and lymphedema stage. These observations imply that hypovitaminosis D may contribute to breast cancer pathogenesis and modulate the risk of treatment-associated morbidities, particularly lymphedema progression. Therefore, it is recommended that individuals diagnosed with BC or at risk of lymphedema have their serum 25-hydroxyvitamin D concentration checked regularly and take supplements if necessary. Although there are findings that vitamin D deficiency may increase the development and severity of lymphedema, more scientific research is needed.

AUTHOR CONTRIBUTIONS

Gülseren Demir Karakılıç: Designing the study, analyzing the data, writing the manuscript; Melek Aykut Selçuk: Data collection, analyzing the data, collecting, writing the manuscript, All co-authors of the study take full responsibility for the integrity of the final version of the manuscript.

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CONFLICT OF INTEREST

All authors declare no financial conflict of interest.

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