



Bone loss in the affected forearm in patients with breast cancer-related lymphedema: a controlled study

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Abstract

Purpose We aimed to investigate the association between lymphedema and bone mass density (BMD) of affected and unaffected forearms in patients with breast cancer-related lymphedema (BCRL). We also explored whether there was a relationship between any disability and BMD on the affected side.

Methods We evaluated 111 patients (53.75 ± 9.07) with unilateral lymphedema (group 1) and 61 patients (50.90 ± 12.44) without lymphedema (group 2) after breast cancer surgery. BMD was performed by dual-energy x-ray absorptiometry (DXA) in lumbar spine, femoral neck, and distal forearm on both sides. Functional situation was assessed by the Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire.

Results The total Z score ($p = 0.018$), T score ($p = 0.005$), and BMD value ($p = 0.014$) were lower in the affected forearm than the unaffected forearm in group 1. There was no difference between the affected or unaffected sides in the total Z score ($p = 0.394$), T score ($p = 0.518$), and BMD value ($p = 0.629$) in group 2. The DXA measurements in terms of the total forearm Z, T scores, and BMD value on the affected side were statistically significantly different between the groups. There was no difference between groups in the femur neck and lumbar total Z and T scores. There was also a positive correlation between the QuickDASH scores and lymphedema stage ($r = 0.469$, $p = 0.001$) and the duration without treatment of lymphedema ($r = 0.298$, $p = 0.02$) in group 1.

Conclusion We recommend early diagnosis and treatment of lymphedema for the protection of upper extremity disability and localized osteoporosis in patients with BCRL.

Keywords Lymphedema · Osteoporosis · Local bone loss · QuickDASH · Quality of life

Due to earlier diagnosis and developments in treatment, breast cancer (BC) is no longer considered to be a life-threatening condition; rather, it is a chronic condition in which health care professionals are able to manage the long-term complications, such as lymphedema (LE) and osteoporosis (OP).

The abnormal build-up of protein-rich fluid in the interstitium because of the obstruction of lymphatic drainage [1] is called LE. In developed regions, the cause of upper extremity

LE is BC [2]. Depending on the type of surgery, axillary lymph node dissection and use of radiation therapy, upper extremity LE can be seen in up to 30% of BC survivors [2, 3]. Various problems may also occur in the affected arm of patients with breast cancer-related lymphedema (BCRL), such as limiting the range of motion, weakness, paresthesia, dysesthesia, and pain due to cervical radiculopathy, brachial plexopathy, and peripheral neuropathy [4].

BC treatments can also cause significant bone loss and increase the risk of fracture [5]. While some chemotherapy drugs can have a direct effect on bone health, other drugs may cause the onset of early menopause in women who are physiologically close to menopause, which may indirectly cause significant bone loss [6]. Additionally, lowering of estrogen levels via aromatase inhibitors, such as anastrozole, exemestane, and letrozole which prevent the formation of estrogen may lead to bone loss during therapy [7]. On the contrary, other hormonal therapies known as selective estrogen receptor modulators (SERMs), including tamoxifen,

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raloxifene, and toremifene can help to protect bones by slowing bone loss [8].

As far as we are aware, there is no study in the literature that compares the bone mineral density (BMD) of affected and unaffected side forearm in patients with BCRL. The current study investigated the association between lymphedema and the BMD of the affected forearm of a group of patients with BCRL compared with a control group of BC patients who did not have lymphedema. In order to identify this relationship and test our hypothesis, we aimed to answer the following five questions: (1) Is there any difference between the affected arm and the unaffected arm of the same patient in regard to the BMD score?, (2) is there any difference between the arms of the participants in the two groups with and without lymphedema in regard to the BMD score?, (3) do the upper extremity disabilities differ between the two groups?, (4) is there any relationship between the lymphedema duration and the BMD scores?, and (5) is there any relationship between any disability and BMD in the affected arm?

Methods

Patient population

This cross sectional-controlled study was conducted with female patients who had undergone mastectomy or breast conserving surgery with unilateral axillary lymphadenectomy for BC. Between April 2016 and November 2016, we evaluated 225 patients. Forty-one patients were excluded due to not meeting the inclusion criteria, and 12 patients did not wish to join the study; thus, a total of 172 women were considered as eligible for the study. There were 111 patients with unilateral

arm lymphedema, which was assessed according to the criteria from the 2016 Consensus Document of the International Society of Lymphology (group 1), and there were 61 subjects without lymphedema (group 2) [1] (Fig. 1). None of our patients had ever been diagnosed with osteoporosis before, also none of them use any treatment for osteoporosis before.

The exclusion criteria were having bilateral BC, bilateral lymphedema, primary and secondary edema (cardiovascular, hepatic, renal, infective, dysmetabolic, etc.), or secondary osteoporosis (chronic kidney disease, hypogonadism, medications, hyperthyroidism, vitamin D deficiency, primer hyperparathyroidism, etc.). All the women who fulfilled the criteria and agreed to participate gave their informed consent in written format. This study conformed to the principles of the Helsinki Declaration, and approval of the local ethics committee of the medical institution was obtained prior to the study.

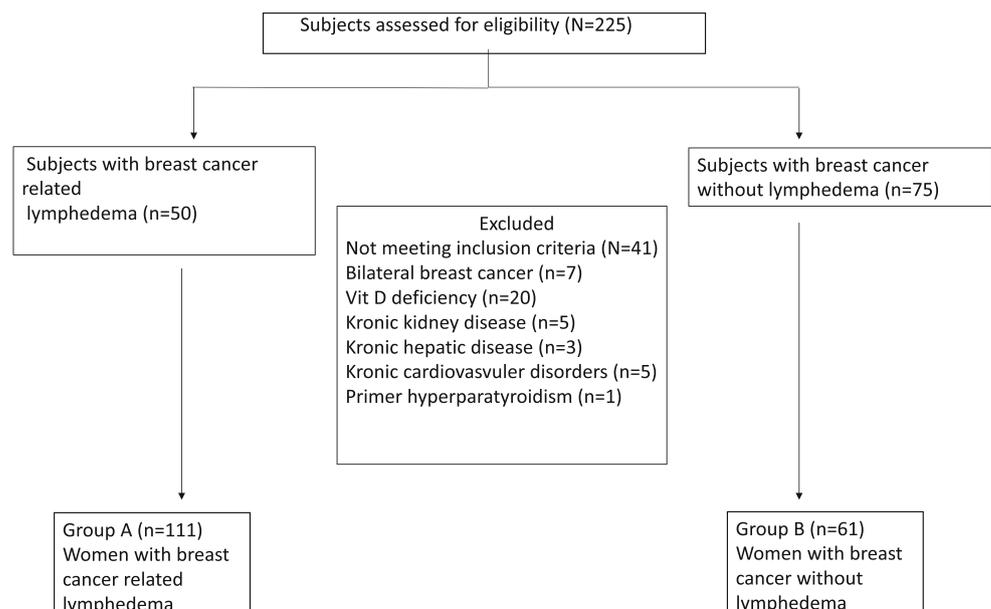
Study design

We used a cross sectional-controlled study design with two groups (Fig. 1). A single researcher (SV) undertook all the clinical assessments.

Clinical records

The demographic and clinical characteristics were recorded and included age, education level, dominant side, affected side, body mass index, age of menopause, medication history, type of cancer, duration of cancer, history of bone fracture, history of metastasis, type of surgery, number of lymph nodes removed, number of positive lymph nodes, stage of lymphedema (sub-clinical, reversible, spontaneous irreversible, and elephantiasis), and grade of lymphedema according to percentage of difference

Fig. 1 Flow diagram for subject enrollment in this study



[minimal (> 5–< 20% increase in limb volume), moderate (20–40% increase), or severe (> 40% increase)] [9], duration without lymphedema treatment, time interval between surgery and lymphedema development, and duration of lymphedema.

The estimated volumes for upper arm and forearm were assessed using the truncated cone method, in which the circumference of the right and left arms were measured at 4-cm intervals, starting from the carpometacarpal joint. This method was previously reported to be reliable and specific [10].

Outcome measures

QuickDASH

The patients' functional situation was assessed by the Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire [11], which is a self-reported assessment tool for the measurement of physical function and symptoms in individuals with a musculoskeletal disorder of the upper limb. The scores indicate the level of disability and severity, ranging from 0 (no disability) to 100 (most severe disability).

Bone mineral density measurement

BMD was performed by dual-energy x-ray absorptiometry (DEXA) (Hologic, QDR 4500, Orlando, USA) in lumbar spine, (L2-L4), femoral neck, and distal forearm on both sides. To reduce any possible error, the same operator with experience assessed all the measurements using the same equipment following standard procedures.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows version 23.0 (SPSS Inc., Chicago, IL). The descriptive statistics were obtained as mean \pm standard deviation and median for continuous and categorical variables, respectively and presented in the form of numbers (*n*) and percentages (%). The Kolmogorov-Smirnov test was used for the normal distribution of the data. Nonparametric tests were used for comparisons between the patient and control group (Mann-Whitney *U* test or Chi-square test, when appropriate). Correlation analysis was conducted using the Spearman test statistics. Whether the effects of clinical characteristics on QuickDASH scores within case group were statistically significant or not was evaluated by univariate linear regression analyses. Determining the best predictor(s) which effect on QuickDASH scores was performed by multiple linear regression analysis after adjustment for all confounding factors. Coefficient of regression, 95% confidence intervals and *t* statistics for each independent variable were also calculated. Due to not being normally distributed, the logarithmic transformation was done for

QuickDASH scores in linear regression analyses. Results with a *p* value of < 0.05 were considered statistically significant.

Results

The mean age of the patients was 53.7 ± 9.0 in group 1 and 50.9 ± 12.4 in group 2 (Table 1). There were no statistically significant differences between age, age of onset of menopause, and the body mass index of the participants in the two groups (*p* > 0.05).

In group 1, the mean duration of lymphedema was 38 months, and the median duration of lymphedema was 8.0 months. There was no difference between the groups in terms of the dominant hand side, affected side, educational level, cancer duration, use of tamoxifen and aromatase inhibitor, the number of dissected lymph nodes, the number of positive lymph nodes, the number of patients with distant metastasis, and history of bone fracture. Patients with BCRL had higher QuickDASH scores than those without BCRL (*p* < 0.0001).

The total *Z* score (*p* = 0.018), *T* score (*p* = 0.005), and the BMD (g/cm^2) value were lower in the affected forearm than the unaffected forearm in group 1 (*p* = 0.014). There was no difference between the affected or unaffected forearms in terms of the total *Z* score (*p* = 0.394), *T* score (*p* = 0.518), and BMD (g/cm^2) value (*p* = 0.629) in group 2.

The DXA measurements in terms of the total forearm *Z*, *T* scores, and the BMD value in the affected limb were statistically significantly different between the groups (Table 2).

There was no difference between groups 1 and 2 in terms of the femur neck and lumbar total *Z* and *T* scores (Table 3). While the femur neck BMD values was similar in both groups (*p* = 0.412), the lumbar BMD values were higher in patients with lymphedema (group 1) than those without lymphedema (group 2) (*p* = 0.029).

Weak negative correlations were found in the total BMD of forearm ($r = -0.238$, *p* = 0.030; $r = -0.312$, *p* = 0.001), *Z* score ($r = -0.259$, *p* = 0.018; $r = -0.199$, *p* = 0.036), *T* score ($r = -0.262$, *p* = 0.016; $r = -0.307$, *p* = 0.001), and the lymphedema duration without treatment and lymphedema stage, respectively.

There was also positive correlation between the QuickDASH scores and lymphedema stage ($r = 0.469$, *p* = 0.001) and the duration without treatment of lymphedema ($r = 0.298$, *p* = 0.02) in group 1.

In univariate analyses, the duration of cancer, status of metastasis, type of surgery (modified radical mastectomy vs radical mastectomy), duration of lymphedema, stage of lymphedema, and duration without treatment were analyzed; and stage of lymphedema (*p* < 0.001) duration without treatment (*p* = 0.006) were found significantly different. At the end of multivariate analyses, status of metastasis (*p* < 0.001), type of

Table 1 Comparison of demographic and clinical characteristics of the two groups

| Variables | Group 1 (n, 111) | Group 2 (n, 61) | p value |
|---|-------------------------|------------------------|------------|
| Age, mean ± SD (min-max) (years) | 53.75 ± 9.07 (34–74) | 50.90 ± 12.44 (33–76) | 0.238 |
| Age of onset of menopause, mean ± SD (min-max) | 47.35 ± 3.37 (40–57) | 48.90 ± 5.54 (37–54) | 0.651 |
| Educational level, low/high, n (%) | 74/37 (66.7/33.3) | 45/16 (73.3/26.7) | 0.522 |
| BMI (kg/m ²) (min-max) | 29.9 ± 6.6 (20.1–28.4) | 28.9 ± 6.3 (21.6–28.4) | 0.431 |
| Duration of cancer, month, mean (min-max) | 63.42 (6–312) | 38.95 (5–180) | 0.321 |
| Status of metastasis, n (%) | 26 (23.4) | 11 (18.03) | 0.378 |
| Type of surgery, n (%) | | | |
| Radical mastectomy, n (%) | 12 (10.8) | 4 (6.5) | |
| Modified radical mastectomy, n (%) | 84 (75.7) | 50 (82) | |
| Breast conserving surgery, n (%) | 15 (13.5) | 7 (11.5) | |
| Number of dissected lymph node mean ± SD (min-max) | 17 ± 3(0–23) | 9 ± 7 (0–16) | 0.492 |
| Number of positive lymph node, mean ± SD (min-max) | 3.00 ± 3.93 (0–17) | 2.28 ± 2.261 (0–7) | 0.535 |
| Number of patients with distant metastasis, n (%) | 14 (12.61) | 8 (13.11) | 0.245 |
| Number of patients with history of bone fracture, n (%) | 3 (2.70) | 1 (1.63) | 0.845 |
| Tamoxifen users, n (%) | 56 (50.40) | 24 (39.34) | 0.422 |
| Aromatase inhibitor users, n (%) | 37 (33.33) | 15 (24.59) | 0.122 |
| QuickDASH scores, mean ± SD (min-max) | 29.07 ± 21.88 (0–70.40) | 4.23 ± 9.94 (0–43) | p < 0.0001 |
| Duration of lymphedema, month, mean ± SD (min-max) | 38.07 ± 42.41 (0–170) | | |
| Time without treatment, month, mean ± SD (min-max) | 8.03 ± 8.94 (0–50) | | |
| ILS - lymphedema stage | | | |
| Stage 0, n (%) | 6 (5.4) 14 | | |
| Stage 1, n (%) | 55 (49.5) | | |
| Stage 2, n (%) | 36 (32.4) | | |
| Stage 3, n (%) | 14 (12.6) | | |

SD standard deviation, n number of patients, min minimum, max maximum. Significance at p < 0.05

surgery (p = 0.039, for radical mastectomy), stage of lymphedema (p < 0.001), and duration without treatment (p = 0.002) were found to be independent risk factors for QuickDASH scores in group 1 (Table 4).

Discussion

The increase in treatment options and the success of treatments have increased survival for BC patients. As such, the

Table 2 Comparison of forearm bone mineral density measurements of both groups

| | Group 1 | p ^a | Group 2 | p ^a | p ^b |
|---------------------------------|------------------------|----------------|------------------------|----------------|----------------------|
| Forearm total T score | | | | | |
| Affected limb | − 1.50 (− 2.20/− 0.10) | 0.005 | − 0.15 (− 1.57/0.67) | 0.612 | 0.013 [#] |
| Normal limb | − 0.78 (− 1.80/0.60) | | − 0.75 (− 1.15/− 0.20) | | 0.643 |
| Forearm total Z score | | | | | |
| Affected limb | − 0.35 (− 1.40/0.80) | 0.018 | 0.37 (− 0.47/1.27) | 0.430 | 0.033 [#] |
| Normal limb | 0.07 (− 0.50/0.80) | | 0.09 (− 0.40/0.65) | | 0.521 |
| Forearm total g/cm ² | | | | | |
| Affected limb | 0.47 (0.43/0.56) | 0.014 | 0.55 (0.48/0.59) | 0.503 | < 0.002 [#] |
| Normal limb | 0.51 (0.47/0.58) | | 0.55 (0.47/0.61) | | 0.351 |

Variables: median (quartile)

Significance at p < 0.05

[#] Mann-Whitney U

^a Intragroup side to side

^b Intergroup comparison

Table 3 Comparison of the femur neck and lumbar total bone mineral density measurements of both groups

| Variables | Group 1 Median (quartile) | Group 2 Median (quartile) | <i>p</i> [#] |
|--------------------------------|------------------------------|------------------------------|-----------------------|
| Femur neck <i>T</i> scores | − 0.90 (− 1.70/− 0.10) | − 0.95 (− 1.83/− 0.21) | 0.719 |
| Femur neck <i>Z</i> scores | − 0.14 (− 0.80/0.40) | − 0.04 (− 1.01/0.51) | 0.510 |
| Femur neck g/cm ² | 0.82 (0.71/0.92) | 0.85 (0.77/0.93) | 0.641 |
| Lumbar total <i>T</i> score | − 1.60 (− 2.21/− 1.17) | − 1.65 (− 2.44/− 1.23) | 0.623 |
| Lumbar total <i>Z</i> score | − 0.51 (− 1.13/0.51) | − 0.48 (− 1.28/0.27) | 0.346 |
| Lumbar total g/cm ² | 0.87 (0.80/0.93) | 0.77 (0.68/0.92) | <i>p</i> = 0.029 |

[#] Mann-Whitney *U*

Significance at *p* < 0.05

importance of the care of survivors and the evaluation of the risks are increased. There is limited data on the association between BMD and lymphedema, although it is known that lymphedema, osteopenia, and osteoporosis increase after BC treatment [12].

In this study, the affected arm BMD and *T* and *Z* scores were lower than the unaffected arm in the patients with BCRL in contrast to the results of the patients without BCRL. There was no difference between the two groups in femur neck scores. As lymphedema duration and stage increased, the affected arm BMD scores were lowered in the patients with BCRL. We also demonstrated that as expected, the QuickDASH scores were higher in patients with BCRL.

In our study, none of patients had osteoporosis-related complications at the beginning. During our study, lymphedema patients with osteoporosis were initiated had bisphosphonates treatment. Despite osteoporosis treatments, in our follow-ups, within first year, two patients had broken their forearms with low energy trauma on their affected side. Fracture of the forearm of our patients resulted with decreased functional capacity and increased lymphedema stages.

The direct relationship between BMD and lymphedema development is a less researched area. It is well known that BC treatments increase the risk of lymphedema, osteopenia, osteoporosis, and bone fracture [13, 14]. The most important factors that reduce BMD scores are chemotherapy, aromatase inhibitor use, and ovarian suppression due to LH-RH agonists [15]. In our study, the groups had similar treatment characteristics. There were no differences in terms of chemotherapy, tamoxifen, and aromatase use. These factors are considered to affect bone health systematically. However, our findings provided a rather thought-provoking local result in that group 1 comprising patients with lymphedema revealed significant differences in *T* and *Z* scores and BMD (g/cm²) between the upper extremities, but no such difference was found in the group 2 patients who did not have lymphedema. Interestingly, there was no difference between the groups regarding the lumbar and femur neck scores. These findings indicate that although the utilization and systematic effects

of treatments and the subsequent bone loss were similar in both groups (shown by similar scores in the femur neck and lumbar BMD), the patients who had lymphedema had additional bone loss in their affected extremities. Therefore, this bone loss on the affected side may not be related to systemic factors, such as use of chemotherapy, tamoxifen, and aromatase inhibitors; rather, some local factors in the arm with lymphedema may be responsible for this difference.

To our knowledge, there is no study in the literature concerning lymphedema as a risk factor for generalized or localized osteoporosis. However, there have been various studies that evaluated localized bone loss as another asymmetric involvement situation of hemiplegia [16–19]. It was reported that patients with hemiplegia had lower BMD scores at the second metacarpal bone, humerus, radius, proximal hip, and total hip on the affected side at the seventh and 12th months [17–19]. Sato et al. evaluated bone loss on the affected side with chronic stroke patients and showed that physical inactivity as a result of immobilization and paralysis might be the primary cause of the decreased bone mass [19]. Thus, the authors found that there was a difference in the pathogenesis of reduced BMD between the stroke patients in the early and long-term groups. These studies demonstrated that immobility or restricted mobility is a major factor of localized osteoporosis in hemiplegia. In the present study, we also interpreted that this localized bone loss might be related to the relatively less use of the affected extremity. We believed that lymphedema might be considered as a restricted mobility status because patients do not use the affected extremity because of fear or avoidance behavior. Hemiplegic patients are not able to move their extremities in full capacity due to motor deficits but in lymphedema, although there is no motor deficit, patients tend to not to move their arms because the arm with lymphedema is heavier than normal arm, and this makes it harder to move. In addition, patients feel the need to protect the arm; so, they hesitate to move them. This fear avoidance behavior results in restricted mobility, and we suggest that this may lead to loss of localized bone mass eventually becoming like a hemiplegic extremity.

Table 4 The univariate and multivariate analyses of factors for QuickDASH scores in group 1

| | Univariate linear regression analyses | | | | | Multiple linear regression analysis | | | | |
|----------------------------|---------------------------------------|---------------------|-------------|----------|----------------|-------------------------------------|---------------------|-------------|----------|----------------|
| | <i>B</i> | 95% CI for <i>B</i> | | <i>t</i> | <i>p</i> value | <i>B</i> | 95% CI for <i>B</i> | | <i>t</i> | <i>p</i> value |
| | | Lower limit | Upper limit | | | | Lower limit | Upper limit | | |
| Duration of cancer | 0.002 | −0.002 | 0.006 | 0.898 | 0.371 | – | – | – | – | – |
| Status of metastasis | −0.960 | −1.946 | 0.026 | −1.930 | 0.056 | −1.459 | −2.296 | −0.621 | −3.455 | < 0.001 |
| Type of surgery* | | | | | | | | | | |
| MRM | 0.295 | −0.373 | 0.964 | 0.876 | 0.383 | 0.343 | −0.179 | 0.865 | 1.302 | 0.196 |
| RM | −0.032 | −0.956 | 0.891 | −0.070 | 0.945 | −0.930 | −0.815 | −0.046 | −2.087 | 0.039 |
| Duration of lymphedema | 0.005 | −0.001 | 0.010 | 1.750 | 0.083 | 0.006 | −0.001 | 0.012 | 1.821 | 0.071 |
| Lymphedema stage | 0.731 | 0.465 | 0.996 | 5.456 | < 0.001 | 0.571 | 0.319 | 0.822 | 4.495 | < 0.001 |
| Duration without treatment | 0.040 | 0.012 | 0.067 | 2.811 | 0.006 | 0.041 | 0.016 | 0.066 | 3.233 | 0.002 |

B coefficient of regression, *CI* confidence interval, *RM* radical mastectomy, *MRM* modified radical mastectomy, *BCR* breast conserving surgery

*BCR group was selected as reference group and MRM and RM groups were evaluated according to BCR group

Another cause of bone loss seen in lymphedema may be the immune-mediated cells and cytokines. Impairment in the lymphatic draining capacity leads to an accumulation of interstitial fluid and tissue swelling, which is known as lymphedema [20]. As a result, oxygen tension is reduced, leading to chronic inflammation and reactive tissue fibrosis, conditions that have been attributed to T helper immune response initiated because of lymphatic stasis [21]. The involvement of the immune system in different inflammatory bone and joint pathologies; e.g., osteoporosis and rheumatoid arthritis is well known with the former being the most common example for inflammatory bone loss, in the development of which T helper (Th) cells have a major role [20]. In the light of these pathophysiologic mechanisms, this T lymphocytic immune incapacity may result in localized chronic inflammation and localized bone resorption called immunoporosis in lymphedema patients [20]. Therefore, in our two groups of patients, this regional osteoporosis may be related to localized inflammation due to the lymphatic stasis. Lymphedema duration without treatment and lymphedema stage were also found to be related with BMD. This prolonged impaired immune response may have resulted in local osteoporosis.

Another example of local bone loss may be complex regional pain syndrome (CRPS), in which the underlying pathology of local bone loss is related to the activation of the sympathetic nervous system activation in connection with bone turnover [22]. Furthermore, the effects of sympathetic nervous system on tissue blood flow and increased inflammatory mediator levels leading to osteoclast activation are considered to be potential causes of bone loss [23, 24]. In this study, we showed localized bone loss in affected extremity as seen in CRPS patients. This localized bone loss may also be related to localized inflammation due to the lymphatic stasis in CRPS.

We also found that forearm BMD was correlated with both the lymphedema stage and the lymphedema duration without treatment in the patients with BCRL. This is a novel finding which may reveal a lymphedema and BMD association. We think that the delay in diagnosis and treatment of lymphedema may locally affect bone mass and BMD scores.

In this study, we found that the level of disability of patients with lymphedema was higher compared to patients without lymphedema, which is in agreement with the literature [25, 26]. We showed that an increased stage of lymphedema was strongly associated with higher disability.

The main strength of the current study was the similar group characteristics according to demographic and clinical data, such as the treatment path and the patients being older. Older age has been reported as a risk factor for lesser use of upper extremity in patients with BCRL [27–29]. Similar to our results, Bojinovic-Rodic reported that the presence of BCRL affects upper limb functions, but their data did not show any correlation between the size of the edema and their upper limb function scores [30]. It is important to note that BC treatment may cause functional limitation of the upper extremity in the absence of lymphedema. Disability in BC patients may be due to different determinants, such as history of chemotherapy and radiotherapy, stage of disease, and grade of neoplasm [29]. According to our data, there was also a significant relationship between the QuickDASH scores and the duration of lymphedema without treatment. We think that the delay in diagnosis and treatment of lymphedema may negatively affect the upper extremity disability.

This is also the first study to show the relationships between lymphedema stage, the duration without treatment, and upper extremity disability. We recommend early diagnosis of lymphedema and early onset of treatment for the protection of upper extremity disability and localized osteoporosis in patients with BCRL.

We had no prospective data about BMD of patients before and after BC treatment or before and after development of lymphedema, which constitutes the major limitation of our study. We also did not evaluate some factors that have been shown to be associated with lymphedema, such as the physical activity level of the patients.

In conclusion, forearm BMD on the affected side is related to local factors, such as lymphedema duration and stage. We also showed that lymphedema may be responsible in the etiology of bone loss in the affected arm due to the disability of the extremity. Early treatment of lymphedema and arm exercises may limit the development of bone loss in the affected arm. Further prospective investigations are needed to reveal the involvement of lymphedema and arm disability in the localized bone loss of patients with BCRL.

Compliance with ethical standards

The corresponding author has full control of all primary data and agrees to allow the journal to review the data if requested.

Conflict of interest The authors declare that they have no conflict of interest.

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