ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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Meme Kanserine Bağlı Lenfödemde Biseps Kas Kalınlığı ve Kutanöz Sertliğin Ultrasonografik Değerlendirilmesi

Ultrasonographic Evaluation of Biceps Muscle Thickness and Cutaneous Stiffness in Breast Cancer Related Lymphedema

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ÖZ

Giriş: Bu çalışmada meme kanseri sonrası kolda sekonder lenfödem gelişen olgularda biseps kas kalınlığı ve kutanöz sertliğin ultrasonografi ile değerlendirilmesi ve klinik bulgularla ilişkisinin araştırılması amaçlandı.

Yöntem: Yaş ortalaması 52 olan 30 hasta, etkilenmemiş ve lenfödemli kollar karşılaştırılarak değerlendirildi. Çevresel ölçümlerden kol hacimleri ve ödem oranları hesaplandı. Lenfödemi değerlendirmek için ultrasonografi kullanıldı ve cilt-cilt altı doku kalınlığı, kompresyonlu ve kompresyonsuz komplians oranı, ekojenite, ekosuz alan ve kayma dalgası elastografisi ölçüldü. Biseps kas kalınlığı ölçüldü. Klinik olarak Lenfödem Yaşam Kalitesi Ölçeği uygulandı.

Bulgular: Olguların çoğu evre 1 (%63,3) ve evre 2 (%33,3) lenfödeme sahipti. Etkilenmemiş ve lenfödemli kolların hacimlerinde istatistiksel olarak anlamlı bir fark bulundu ($p<0,001$) ve ödem oranı $0,23\pm0,22$ idi. İki kol arasında cilt-cilt altı elastografi ve komplians oranı açısından anlamlı bir fark bulunmadı ($p>0,05$). Lenfödemli kolun biseps kas kalınlığı etkilenmemiş kola kıyasla anlamlı derecede daha inceydi ($p=0,025$).

Sonuç: Deri-cilt altı elastografi ve komplians oranı değerlerindeki benzerlik, bu olgularda ileri evre lenfödem-fibrozis gelişmediğini düşündürmekte ve lenfödemin klinik evrelemesini desteklemektedir. Biseps kas kalınlığındaki belirgin azalma, ileri evre lenfödem olmadan da ortaya çıkabilen sarkopeniye işaret etmektedir. Bu durum, meme kanseri hastalarında olası lenfödemi önlemek için ameliyat sonrası erken dönemden itibaren düzenli egzersizin, özellikle de kuvvet antrenmanının önemini vurgulamaktadır. Lenfödem vakalarında sarkopeni ve egzersiz tedavisi konusunda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: lenfödem, ultrasonografi, sarkopeni, elastisite görüntüleme teknikleri, meme kanseri

ABSTRACT

Objective: This study aims to evaluate biceps muscle thickness and cutaneous stiffness using ultrasound in cases of secondary lymphedema in the arm following breast cancer and to investigate their relationship with clinical findings.

Method: Thirty patients, with an average age of 52 years, were assessed comparing the unaffected and lymphedematous arms. Arm volumes and edema ratios were calculated from circumferential measurements. Ultrasonography was used to assess lymphedema, measuring skin-subcutaneous tissue thickness, compliance ratio with and without compression, echogenicity, echo-free space, and shear wave elastography. Biceps muscle thickness was also measured. Clinically, the Lymphedema Quality of Life Scale was applied.

Results: Most cases had stage 1 (63.3%) and stage 2 (33.3%) lymphedema. A statistically significant difference was found in the volumes of the unaffected and lymphedematous arms ($p<0.001$), with an edema ratio of 0.23 ± 0.22. No significant difference was found between the two arms in skin-subcutaneous elastography and compliance ratio ($p>0.05$). The lymphedematous arm had significantly thinner biceps muscle thickness compared to the unaffected arm ($p=0.025$).

Conclusion: The similarity in skin-subcutaneous elastography and compliance ratio values suggests that advanced-stage lymphedema-fibrosis has not developed, supporting the clinical staging of lymphedema in these cases. The significant decrease in biceps muscle thickness indicates sarcopenia, which may occur even without advanced-stage lymphedema. This underscores the importance of regular exercise, especially strength training, from the early postoperative period in breast cancer patients to prevent potential lymphedema. Further research on sarcopenia and exercise therapy in lymphedema cases is needed.

Keywords: lymphedema, ultrasonography, sarcopenia, elasticity imaging techniques, breast cancer

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INTRODUCTION

Breast cancer is acknowledged as one of the most prevalent types of cancer among women worldwide. The treatment of breast cancer involves various methods such as surgical intervention, chemotherapy, and radiotherapy, with potential positive impacts on patients' lifespan and quality of life. However, as a side effect of breast cancer treatment, lymphedema can develop. Lymphedema is a condition caused by impaired lymphatic circulation and is typically characterised by the accumulation of protein-rich interstitial fluid. (1)

Lymphedema is classified into primary (congenital) and secondary (acquired) types. Secondary lymphedema, particularly associated with cancer treatment, is common in developed countries. Breast cancer, one of the most common cancers in women, holds special significance regarding the risk of lymphedema. Every woman undergoing cancer treatment carries a lifelong risk of developing lymphedema. Therefore, early detection of lymphedema is crucial, and an effective treatment protocol should be established. (2)

Lymphedema can negatively impact not only physically but also affect muscle functions. When combined with nerve impairments induced by treatments like radiotherapy and chemotherapy for cancer patients, it can lead to further complications. (3)

Measurements conducted with a tape measure are commonly used in the clinical assessment of lymphedema. (4,5) However, these measurements are insufficient in distinguishing between skin, subcutaneous tissue, and muscle. Therefore, the effects of lymphedema on the skin and subcutaneous tissue need to be better understood using devices such as ultrasonography. (6)

Despite being an age-related condition, sarcopenia can affect many individuals and detrimentally impact their quality of life. (7,8) Sarcopenia that may occur in advanced lymphedema can negatively affect upper extremity functions and influence the response to treatment. Therefore, assessment of sarcopenia plays a critical role in the diagnosis and response to treatment in lymphedema. Biceps muscle thickness measurement through ultrasonographic assessment is recommended for evaluating sarcopenia in the upper extremities. (9)

The aim of this study is to assess biceps muscle thickness and cutaneous stiffness using ultrasound in patients with lymphedema in the arm due to breast cancer, and to explore the relationship between these ultrasound measurements and clinical evaluations of lymphedema.

MATERIALS AND METHODS

Study Design

Our cross-sectional study received ethical approval from the Manisa Celal Bayar Faculty of Medicine Health Sciences Ethics Board with approval number 20.478.486/1358 on May 25, 2022. Thirty patients diagnosed with secondary unilateral lymphedema, meeting the inclusion and exclusion criteria, were enrolled through the Physical Medicine and Rehabilitation department of the hospital. Participants were provided with detailed information about the study, and after obtaining their consent, they signed an informed consent form that our university's Faculty of Medicine Ethics Committee had approved.

Inclusion Criteria: Patients who are female and range in age from 18 to 65. Diagnosis of unilateral lymphedema secondary to breast cancer treatment. At least a 2 cm circumference difference in at least one region compared to the normal side in circumferential measurements.

Exclusion Criteria: Male and pediatric patients, pregnant women, presence of active infection, individuals with peripheral nerve damage, with uncontrolled cardiac problems

Outcome Measurements

In our study, two groups were formed to compare the lymphedematous arm with the unaffected arm in 30 patients diagnosed with lymphedema. Demographic information and Lymphedema Quality of Life Questionnaires (LYMQOL-ARM) results were recorded using a case follow-up form.

Circumferential measurements, considered one of the most reliable methods for detecting lymphedema, were taken using a tape measure at 4 cm intervals. These measurements included the metacarpophalangeal region, web space, the ulnar styloid, 4 cm above the ulnar styloid, and continued in 4 cm increments up to the mid-humerus. The limb volumes of the patients' arms were calculated using the Frustum formula based on these measurements, with the limb volume calculator. ($V = 1/3 \times \pi \times h \times (r1^2 + r2^2 + r1 \times r2)$).(10)

Ultrasonography measurements in the study were conducted using the ESAOTE S.p.A Via Enrico Malen 77, 16152 Genova, Italy – MyLabX8 Exp ultrasonography device and a linear high-frequency probe (4-15 MHz). Ultrasonographic measurements, including echogenicity, echo-free space, skin-subcutaneous tissue thickness, and shear wave elastography, were performed at three different points: the midpoint between the lateral and medial epicondyles, 10 cm below, and 10 cm above this point. (11,12) Echogenicity was classified based on the relative brightness of the tissue in comparison to surrounding structures, where hyperechoic tissues appear brighter and hypoechoic tissues appear darker. (13) Echo-free space was defined as areas with no detectable echoes, typically corresponding to fluid-filled or edematous regions. (14) Skin-subcutaneous tissue thickness was measured as the distance from the skin surface to the superficial border of the muscle fascia. The probe was oriented parallel to muscle fibers to obtain shear wave elastography (SWE) measurements in the longitudinal axis and rotated 90 degrees for transverse axis SWE measurements. A thin layer of acoustic gel was applied to the skin during measurements, and the probe was held steady throughout SWE acquisition. (15) (Fig-1) Biceps muscle thickness measurements were taken between the lateral epicondyle of the humerus and the acromial process of the scapula, 60% distal from the lateral epicondyle. (16) (Fig-2)

Edema ratio was calculated using the formula {(extremity volume in the affected limb) - (extremity volume in the contralateral limb)}/(extremity volume in the contralateral limb). (17) The compliance ratio was calculated using the formula (Initial thickness – thickness of compression)/ Initial thickness. (11)

All outcome measurements, including both ultrasonographic elastography and clinical assessments, were conducted by a physiatrist (ZU) with extensive experience exceeding ten years in musculoskeletal ultrasound. Study organization and participant coordination were managed by another investigator (İCÖ). All measurements and questionnaires were completed on the same day to minimize variability and ensure consistency.

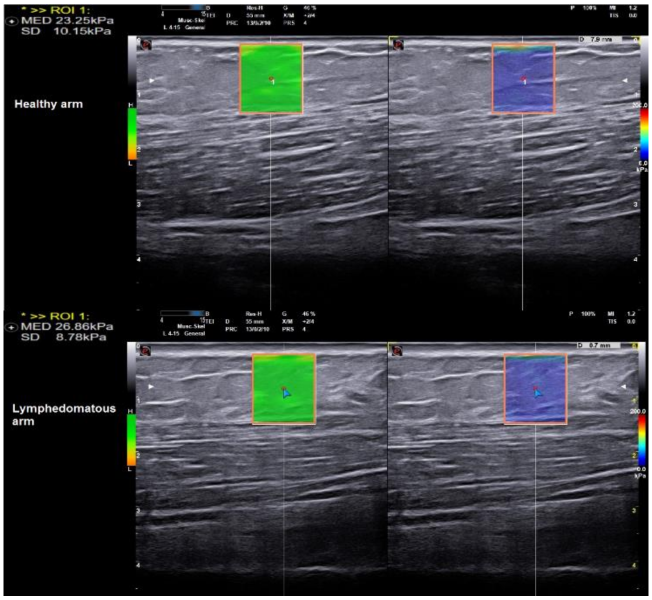

Figure 1. Shear wave elastography measurement

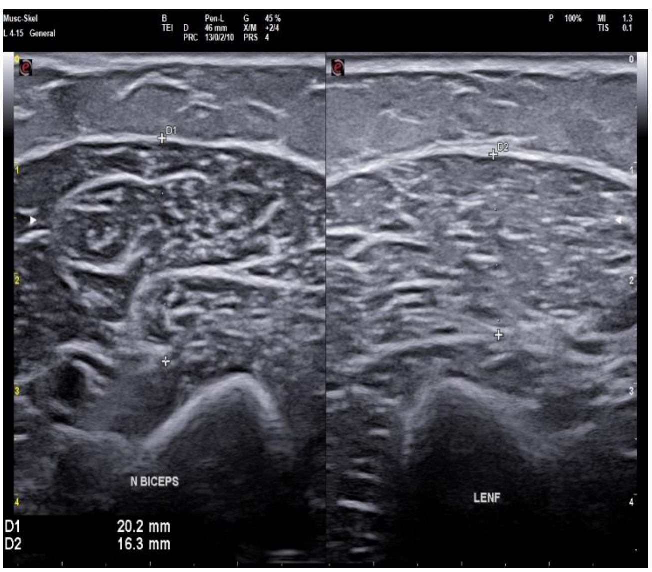

Figure 2. Biceps muscle full thickness measurement

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 24.0 software package. (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.)

For normal-distribution variables, descriptive statistics were shown as mean ± standard deviation; for non-normal-distribution variables, as median (minimum-maximum); and for nominal variables, as the number of subjects (n) and percentage (%). Pearson chi-square test was used to assess nominal variables. The normality of variable distributions was examined visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov).

All data in our study exhibited a normal distribution. Independent variables showing a normal distribution were analyzed using independent samples t-tests, while dependent variables with a normal distribution were analyzed using paired samples t-tests. The Pearson correlation test has been used for the correlation analysis of numerical data. Intraclass correlation coefficient (ICC) analysis was performed to determine the consistency of SWE evaluations.

Results were considered statistically significant for $p < 0.05$.

The sample size calculation was performed considering a power of 0.80, an effect size of 0.80, and a significance level of 0.05 to detect differences in muscle thickness and cutaneous stiffness between the unaffected and lymphedematous arms. Accordingly, a total of 30 patients was deemed necessary for this study. The sample size calculation was conducted using the G*Power 3.1.9.7 program

RESULTS

The sociodemographic data of the patient group included in the study are presented in Table 1.

Using circumferential measurements of the group included in the study, limb volumes were calculated for both the healthy and lymphedematous arms. A statistically significant difference was observed between the two groups ($p < 0.001$). The calculated edema ratio based on limb volumes was found to be 0.23±0.22 (Table 2)

The distribution of echogenicity and echo-free space data on the lymphedematous side of the cases is shown in Table 3. The number of cases with advanced-stage echogenicity increase and echo-free space was quite low.

When SWE values and compliance ratios were compared between the healthy and lymphedematous arms of the study group, no statistically significant difference was observed between the two arms (Table 4).

The comparison between the biceps muscle thickness of the healthy arm and the biceps muscle thickness of the lymphedematous arm in the study group revealed that the biceps thickness of the lymphedematous arm was statistically significantly lower (p=0.025) Figur(Table 5).

Correlation analysis was performed between the difference in biceps muscle thickness on the lymphedematous side and intact side, duration of lymphedema, duration of operation, lymphedema quality of life, limb volume, SWE and compliancy ratio values. No significant correlation was found. The intraclass correlation coefficient for SWE evaluations was found to be 0.859 ($p<0.001$).

Table 1. General Profile Table of Lymphedema Patients		
		Patients group(n:30)
Age (Mean.±SD)(Min-Max)		53.10±12.59 31-85
Education Level (n, %)	Primary education	16 (53.33%)
	High School	4 (13.33%)
	University	8 (26.66%)
	Master's Degree	2 (6.66%)
Dominant Side (n, %)	Right	27 (89.99%)
	Left	3 (9.99%)
Arm Affected by Lymphedema (n, %)	Dominant Arm	18(60%)
	Non-Dominant Arm	12(40%)
Time elapsed since the date of operation (month) (Mean.±SD)(Min-Max)		54.00±34.92 12-144
Age of onset of lymphedema (Mean.±SD)(Min-Max)		52.00±12.43 30-82
Duration of lymphedema (month) (Mean.±SD)(Min-Max)		14.43±21.54 1-72
Lymphedema stage (n, %)	1	19 (63.34%)
	2	10 (33.33%)
	3	1 (3.33%)
Lymphedema quality of life scale (Mean.±SD)(Min-Max)		25.45±17.82 0-84
Operation type	Total mastectomy + lymph node dissection	21 (70%)
	BPS + Lymph node dissection	9 (30%)
Lymph node involvement (n, %)	Yes	26 (86.67%)
	No	4 (13.33%)
Metastasis presence (n, %)	Yes	2 (6.67%)
	No	28 (93.33%)
Chemotherapy Treatment presence (n, %)	Yes	26 (86.67%)
	No	4 (13.33%)
Radiotherapy Treatment presence (n, %)	Yes	26 (86.67%)
	No	4 (13.33%)
Comorbidity (n, %)	Yes	8 (26.67%)
	No	22 (73.33%)
Weight gain (n, %)	Yes	8 (26.67%)
	No	22 (73.33%)
Lymphedema treatment (n, %)	CDT	26 (86.67%)
	No	4 (13.33%)
Standard deviation(SD), Minimum (Min), Maximum (Max), Breast Preventive Surgery (BPS), Complete Decongestive Therapy (CDT)		

Table 2. Limb Volume Comparison and Edema Ratio				
	Arm with Lymphedema (N=30) (Mean.±SD)	Healthy Arm (N=30) (Mean.±SD)	Difference between groups (p-value)	Edema Ratio (Mean.±SD) (Min-Max)
Limb Volume(mls)	2.19±0.56	1.77±0.35	<0.001	0.23±0.22 0.01-0.99
Standard deviation(SD)				

Table 3. Distribution of Ecogenicity (Seg) and Eco-Freespace (Sefs)		
		Arm with Lymphedema (N=30) (n, %)
Seg	0	13 (43.33%)
	1	14 (46.67%)
	2	3 (10.00%)
Sefs	0	16 (53.33%)
	1	11 (36.67%)
	2	3 (10.00%)
Ecogenicity (Seg) Eco-freespace (Sefs)		

Table 4. SWE and Compliance Ratio Comparison						
	SWE(m/sn)			Compliance Ratio		
	Arm with Lymphedema (N=30) (Mean.±SD) (Min-Max)	Healthy Arm (N=30) (Mean.±SD) (Min-Max)	Difference between groups (p value)	Arm with Lymphedema (N=30) (Mean.±SD) (Min-Max)	Healthy Arm (N=30) (Mean.±SD) (Min-Max)	Difference between groups (p value)
10 cm above the middle of the lateral and medial condyle	2.86±1.23 1.10-7.00	2.88±1.19 0.80-5.90	0.932	0.19±0.21 0.03-0.81	0.20±0.23 0.00-0.86	0.680
Middle of lateral and medial condyle	2.61±1.29 0.50-5.71	2.81±1.20 0.80-5.72	0.406	0.23±0.19 0.00-0.74	0.24±0.19 0.06-0.75	0.878
10 cm below the middle of the lateral and medial condyle	3.28±1.29 1.00-5.46	3.24±1.36 0.70-6.50	0.881	0.18±0.21 0.02-0.85	0.29±0.26 0.06-0.88	0.266
Shear wave elastography(SWE), Standard deviation(SD), Minimum (Min), Maximum (Max)						

Table 5. Biceps Muscle Thickness Comparison			
	Arm with Lymphedema (N=30) (Mean.±SD)(Min-Max)	Healthy Arm (N=30) (Mean.±SD)(Min-Max)	Difference between groups (p value)
Biceps Muscle Full Thickness (cm)	18.91±4.09 12.60-28.60	20.03±4.86 12.90-20.03	0.025
Standard deviation(SD), Minimum (Min), Maximum (Max)			

DISCUSSION

Innovative imaging modalities such as ultrasonography and shear wave elastography were used to evaluate the effects of lymphedema on tissue properties in patients who developed lymphedema after breast cancer treatment, revealing important findings. Despite the absence of advanced lymphedema, a significant decrease in biceps muscle thickness was observed in arms with lymphedema. This indicates that muscle atrophy can potentially start early due to disuse or kinesiophobia (fear of movement) and emphasizes the importance of early intervention, especially regular exercise. Furthermore, there is no shear wave elastography study in the current literature evaluating the progression of subcutaneous tissue to fibrosis in patients with lymphedema. In this study, a new perspective on the evaluation of subcutaneous fibrosis with this method is presented. It has been shown that muscle loss can occur in the early stage without a significant change in tissue elasticity, emphasizing the critical role of early strengthening exercises to maintain muscle strength in patients with lymphedema.

The data obtained from the volume calculations of the patients showed a statistically significant volume difference between the affected and unaffected arms, which confirmed the diagnosis of lymphedema. The mean follow-up period was 14.43±21.54 months and it was found that the majority of the patients were diagnosed with stage 1-2 lymphedema according to clinical staging. (1) The results of ultrasonography examination were consistent with this clinical evaluation and it was observed that the patients were generally diagnosed with early stage lymphedema and advanced stage cases were rare. Shear wave elastography and compliance ratio evaluations showed no significant difference between the affected and unaffected arms at the midpoint of the lateral and medial epicondyle and 10 cm above and below this point. These results show that tissue elasticity is similar in both arms, and clinical and ultrasonographic findings support that the patients are in the early stage. In this context, it indicates that early stage lymphedema does not necessarily lead to changes in tissue elasticity or development of fibrosis.(9)

Recent studies have reported that a decrease in muscle size may be an indicator in the assessment of sarcopenia by ultrasonography.(18-20) In this context, the biceps muscle is among the muscles evaluated for sarcopenia.(21) In our study, the biceps muscle thickness of the lymphedematous arm was found to be significantly reduced compared to the healthy arm. This finding suggests that patients may have decreased muscle size due to disuse or kinesiophobia. Immobilization of patients, especially after surgery and during radiotherapy, may also contribute to this situation.

The fact that there was no significant difference in tissue elasticity between the arms with and without lymphedema suggests that there may be a decrease in muscle thickness (sarcopenia) even if advanced in the absence of advanced lymphoedema. Therefore, the importance of regular exercise, especially strengthening exercises, should be emphasized from the postoperative period. Despite the opinions that resistance exercises may be harmful, studies have shown that such exercises have positive effects on patients. (22-23) A study conducted especially in patients who developed lymphedema after gynecologic cancer surgery revealed that resistance exercises contributed to improvement in quadriceps muscle strength. (24) Another study showed that progressive resistance exercises performed in addition to decongestive therapy caused a decrease in arm circumference and an increase in muscle diameter. (25) Similarly, the results of our study confirm that there are significant differences in ultrasound measurements between the arms with and without lymphedema. In this context, it is thought that resistance exercises may play an important role in strengthening muscles and preventing sarcopenia in patients with lymphedema. However, these results need to be further confirmed and supported by larger-scale studies. Our study may be a basic starting point to understand the clinical effects of exercise in patients with lymphedema and to improve their quality of life.

However, the small sample size of our study and the limited number of cases of advanced lymphedema suggest that more extensive studies are needed to confirm these findings and to fully assess changes in tissue flexibility and muscle strength at different stages of lymphedema. Future studies should investigate the effect of structured exercise programs on muscle strength, including objective assessment tools such as hand dynamometers to measure muscle function.

CONCLUSION

This study demonstrates that ultrasonography is an important tool in the evaluation of both clinical and subclinical changes in patients with lymphedema after breast cancer. The decrease in biceps muscle thickness in the lymphedematous arm suggests the potential for early sarcopenia, even in the absence of advanced lymphedema. This highlights the importance of early intervention through regular strengthening exercises to prevent muscle loss and improve patient outcomes. Furthermore, the use of shear wave elastography and compliance ratio assessments offers an innovative approach to the evaluation of tissue properties in lymphedema. Confirmation of these findings with larger-scale studies will help us better understand the role of exercise in preventing sarcopenia and improving quality of life in patients with lymphedema.

Ethics Committee Approval: Ethical approval for the study was obtained from the Celal Bayar University Faculty of Medicine Ethics Committee with approval number 20.478.486/1358 on May 25, 2022.

Author contributions: İ.C.Ö., Z.Ü., E.O., Design: İ.C.Ö., Z.Ü., E.O., Data Collection or Processing: İ.C.Ö., Z.Ü., E.O., Analysis or Interpretation: İ.C.Ö., E.O. Literature Search: İ.C.Ö. E.O., Writing: İ.C.Ö. E.O.

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Informed Consent: Participants were provided with detailed information about the study, and after obtaining their consent, they signed an informed consent form that our university's Faculty of Medicine Ethics Committee had approved.

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