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Is there a correlation between the biceps brachii muscle stiffness measured by elastography and severity of lymphedema in patients with breast cancer-related lymphedema?

Meme kanseri ilişkili lenfödemde lenfödem şiddeti ve elastografi ile ölçülen biseps kası sertliği arasında bir korelasyon var mı?

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Abstract

Aim: Breast-cancer-related lymphedema (BCRL) causes symptoms such as swelling, heaviness, tightness, firmness, pain, numbness, or impaired mobility in affected arm and hand. It also predisposes patients to fibrosis, cellulitis, infections, lymphadenitis, and septicemia. Aim of this study was to analyze correlation between the biceps brachii muscle stiffness measured by shear wave elastography (SWE) and severity of the lymphedema.
Methods: This prospective study included 20 consecutive patients (mean age, 54.6±5.4 years) with having BCRL in the upper limb. Stiffness of the biceps brachii muscle was assessed by SWE. Shear wave speeds (SWS) of the biceps muscle on the affected side for each patient were measured. Severity of the lymphedema was determined by difference between diameters and volumes of affected and unaffected extremities. Correlations between the biceps brachii muscle stiffness measured by SWE and difference between diameters and volumes of affected and unaffected extremities were analyzed.
Results: SWS of the biceps muscle on the affected side showed positive fair correlation with difference between diameters and volumes of affected and unaffected extremities (0.70≥ r≥ 0.51).
Conclusion: Our results suggest that the biceps muscle stiffness increases with increase in severity of lymphedema. The biceps muscle stiffness measured by SWE could provide a quantitative tool for following-up patients with BCRL.

Keywords: Lymphedema, elastography, breast cancer, biceps brachii

Öz

Amaç: Meme kanseri ilişkili lenfödem (MKİL) etkilenen el ve kolda şişme, ağırlık hissi, katılık, ağrı, uyuşukluk ve hareket kısıtlılığına neden olur. MKİL bu olgularda fibrozis, selülüt, lenfadenit ve sepsise yatkınlık yapar. Bu çalışmanın amacı biseps kasında “makaslama dalgası elastografi” (SWE) ile ölçülen sertlik ve lenfödem şiddeti arasındaki korelasyonu değerlendirmektir.
Yöntemler: Üst ekstremitede MKİL olan 20 olgu (ortalama yaş; 54,6±5,4 yıl) prospektif olarak çalışmaya dâhil edilmiştir. Biseps kası sertliği SWE ile değerlendirilmiştir. Her bir olguda etkilenen taraftaki biseps kasında “makaslama dalgası” hız değerleri ölçülmüştür.
Lenfödem şiddetine lenfödemden etkilenen tarafla etkilenmeyen taraf arasındaki hacim ve çap farkı hesaplanılarak karar verilmiştir. Her olguda biseps kasında “Shear Wave” hız değeri (SWH) ölçülmüştür. SWE ile ölçülen biseps kası sertliği ve etkilenen tarafla etkilenmeyen taraf arasındaki hacim ve çap farkları arasındaki korelasyon değerlendirilmiştir.
Bulgular: Etkilenen kolda biseps kasında ölçülen SWH değerleri ile etkilenen ve etkilenmeyen ekstremiteler arasındaki hacim ve çap farkı arasında orta derecede bir korelasyon saptanmıştır (0,70≥ r≥ 0,51).
Sonuç: Çalışmamızda lenfödem şiddeti arttıkça biseps kası sertliğinde artış olduğunu gösterdik. SWE ile ölçülen biseps kası sertliği MKİL tanılı olgularda takipte kullanılabilecek kantitatif bir metot olabilir.

Anahtar Kelimeler: Lenfödem, elastografi, meme kanseri, biseps

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Introduction

Breast cancer-related lymphedema (BCRL) is one of the most common complications of breast cancer survivors. It occurs as a result of fluid accumulation in the interstitial tissue due to damage of the lymphatic system, induced by surgery and/or radiation, or tumor-induced neo-lymphangiogenesis [1]. BCRL causes upper limb swelling, pain, immobility and it seriously affects the quality of life [2-4].

Pathologic processes such as chronic inflammation with fibrosis, increased cellularity and desmoplastic reaction in neoplastic diseases alter tissue ultrastructure and stiffness [5]. Ultrasound (US) elastography is a non-invasive, inexpensive, and useful complementary tool that allows measuring tissue stiffness and it also improves the diagnostic performance of B-mode US [6]. Recently elastography is being used in imaging of many tissues including breast, thyroid, liver, lymph nodes and musculoskeletal tissues in clinical practice. Presently, two main US elastography techniques are used in clinical practice: strain elastography (SE) and shear wave elastography (SWE). SE uses manual compression produced by operator pressing the transducer and provides qualitative and semiquantitative analysis of the lesions. SE measures the displacement of tissue and it can be affected by the degree of compression. SWE is one of the dynamic elastography techniques which use shear waves generated by acoustic radiation force [7]. SWE enables quantitative analysis of tissue elasticity without compression and it is more objective than the SE [7, 8].

Several imaging techniques have been used for qualitative assessment of lymphedema. Lymphoscintigraphy is a standard diagnostic imaging modality in which the lymphatic system in the affected limb can be demonstrated by a radiotracer [9]. The main problem with lymphoscintigraphy is the poor spatial resolution of the images. Indocyanine green (ICG) fluorescence lymphangiography is another imaging technique using near infrared technology. ICG fluorescence lymphangiography allows evaluating the superficial lymphatics and it is a baseline imaging modality for deciding on surgical intervention. The main disadvantage of fluorescence lymphangiography is being an intraoperative procedure [10]. Contrast-enhanced MR lymphography is another invasive imaging modality and it remains as an experimental study [11]. Previously US have been shown to be a reliable imaging modality by comparing the thickness of the skin and subcutaneous tissue [12-15]. Both the skin and subcutis are thickened in the ipsilateral swollen arm compared with the contralateral arm, confirming the clinical impression [16]. After breast cancer treatment, not only the lymphatic drainage of the subcutis of the arm both also the lymphatic drainage in the muscle could be affected [17]. There are a few numbers of studies in the literature evaluating lymphedema by elastography. Elastography has been studied in differentiating between lymphedematous and normal tissues and it has been suggested as a feasible method to differentiate normal and lymphedematous tissues by measuring the stiffness of arm and leg subcutis tissue [18, 19]. We aimed to demonstrate the the effects of lymphedema on the muscle tissue. To the best of our knowledge, the stiffness of biceps muscle in patients with BCRL has not been studied yet in the literature.

Herein, we aimed to analyze the correlation between the biceps brachii muscle stiffness measured by Shear Wave Elastography (SWE) and the severity of the lymphedema.

Material and methods

Subjects

This study conforms to the Declaration of Helsinki. The study was approved by the Institutional Review Board and Ethics Committee and supported by the Institutional Research Fund (project number: KA16/150, 2016). Written informed consent was obtained from all patients.

The inclusion criteria were: having unilateral BCRL and clinically detected lymphedema (a circumferential difference of ≥2 centimeter or volumetric difference of ≥ 200 mL, between the affected and non-affected arms). The exclusion criteria were as follows: prior surgery or major trauma to the upper extremity and any other muscular disorders, bilateral breast cancer survivors. Thus, this prospective study included 20 consecutive patients with having BCRL in the upper limb.

Demographic data including age, body mass index (BMI as kg/m2), side of the dominant extremity, duration of time since the diagnosis of breast carcinoma, duration of time since swelling started, received treatment modalities were evaluated.

Assessing lymphedema

The severity of the lymphedema was determined by the difference between the circumferential diameters and volumes of the affected and unaffected extremities. Before taking volumetric and circumferential arm measurements, women were asked to remove all jewelry, compression bandages and compression sleeves from the upper extremity. Water displacement volume method is used to assess the volume of the upper limb.

A larger water container with an overflow pipe drained into a different smaller container. The larger container was filled with warm water up to a mark at the lower border of the overflow pipe. Each arm was placed in the container in turn and the volume of water displaced was recorded as mm3 (Figure 1).

A flexible, non-stretch fabric type measurement tape was used to measure arm circumferences. Measurements were performed at the level of the 10th cm proximal to the lateral epicondyle as mm.

US and SWE examinations

The US and SWE examinations were performed with a US system (Acuson S 2000; Siemens, Erlangen, Germany). SWE was performed by using a probe with an L9-4 linear array. Each patient was examined by the same radiologist (with >3 years of experience in musculoskeletal radiology). The radiologist was blinded to physician's examination.

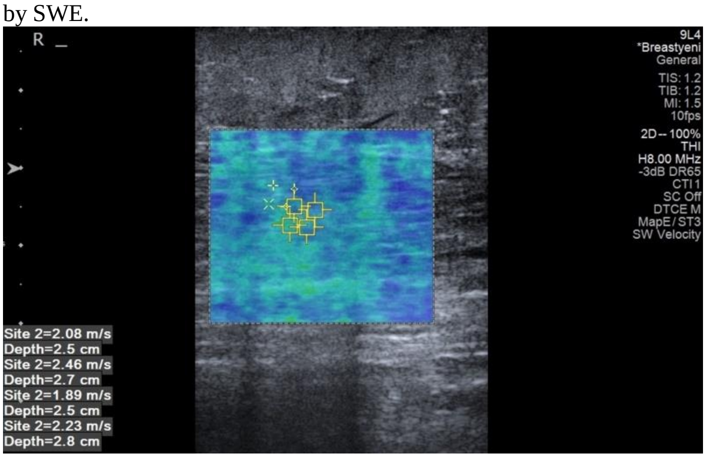
All US and SWE examinations were performed with the patient in the sitting position in front of an examination bed with their arms extended down by their side. The arms were extended and the forearms held in the supine position. Care was taken to examine in a neutral position as much as possible. A standard US examination was initially performed to view the biceps muscle in the axial plane. Longitudinal plane was preferred for SWE measurements to visualize the muscle more widely. A rectangular electronic box-shaped region of interest (ROI) was used for shear wave speed (SWS) measurements automatically provided by the system software (Figure 2). The quality of the images was assessed by color-coded quality maps provided by the US system in which the green areas were considered reliable. The yellow and red color–coded areas were considered as low-quality scans. The scanning was repeated till high-quality images were obtained and the best representative image of the highest quality on the quality map was selected to measure SWS. The stiffness of the biceps brachii muscle was measured by virtual touch tissue imaging quantification method (VTIQ). SWS of the biceps muscle on the affected side for each patient were measured. The correlations between the biceps brachii muscle stiffness measured by SWE and the difference between the diameters and volumes of the affected and unaffected extremities were analyzed.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation. Kolmogorov-Smirnov test was used to test normality of data. The correlation of sonoelastographic findings with the volumes and diameters were assessed by using Pearson correlation coefficient test. The correlation coefficients were interpreted as either excellent r≥0.91; good 0.90≥r≥0.71; fair 0.70≥r≥0.51; weak 0.50≥r≥0.31; or little or none r≤0.3. The significance level was determined at p<0.05. All statistical tests were performed using IBM SPSS Statistics software program (Chicago, IL, USA) for Mac version 20.0.

Figure 1: Assesing volume of the arm by water displacement method.

Figure 2: Shear Wave Speed (SPS) measurement of the biceps muscle by SWE.



Results

The mean age of the study population was 54.6±5.4 years. Mean BMI of the patients was 28.8 ± 20.9 kg/m2. The affected extremity was the dominant extremity in the 14 (70%) of the patients.

Duration of the time since the diagnosis of breast carcinoma was 63.9± 61.5 months, and duration of the time since swelling started ranged from 1 month to 120 months (median 12 months). All the patients had surgery and also all of them received chemotherapy. Nineteen of the patients (95%) had axillary lymph node dissection. Eighteen of the patients (90%) received radiotherapy. The detailed demographic information of the study population is demonstrated in Table.

Mean volumetric difference between the affected and unaffected extremities was 912.62±564.5 mm3. Mean circumferential measure between the diameters of the affected and unaffected extremities was 35.3±1.4 mm.

Mean SWS of the biceps muscle on the affected side was 2.27±0.40m/s. SWS of the biceps muscle on the affected side showed fair positive correlation with the difference between the volumes of the affected and unaffected extremities (r=0.65, p=0.043).

There was a fair positive correlation between the SWS of the biceps muscle on the affected side and the difference between the diameters of the affected and unaffected extremities (r=0.62, p=0.039).

Table 1: Clinical characteristics of the study population.

Characteristics	
Age (years)[¥]	54.6±5.4
Body mass index (kg/m^2)[¥]	28.8±20.9
Duration of time since breast carcinoma diagnosed (months)[¥]	63.9±61.5
Location of tumor[µ]	
Upper outer quadrant	14
Upper inner quadrant	3
Lower outer quadrant	2
Lower inner quadrant	1
Type of breast surgery[µ]	
Modified radical mastectomy	12
Breast conserving surgery	8
Type of axillary lymph node surgery[µ]	
Sentinel lymph node biopsy	19
Level I-II axillary lymph node dissection	17
Radiotherapy[µ]	19
Chemotheraphy[µ]	20
Duration of lymphedema (months)[β]	12 (1-120)

[¥]: mean±standard deviation, [µ]: n, [β]: median (range)

Discussion

This study showed an association between the severity of lymphedema and the stiffness of the biceps muscle. Quantification of lymphedema by measuring limb size or limb volume has been used in both clinical practice and research studies. Among BCRL patients, shoulder and arm diseases including rotator cuff disease, adhesive capsulitis and axillary web syndrome can be seen and these diseases affect the morbidity of both shoulder and arm. Also tendon of the long head of the biceps can be affected in BCRL [20, 21]. Previously, Jang et al. showed bursal thickening and distension of the biceps brachii tendon sheeth among patients with BCRL. Jang et al found that the patients with a supraspinatus tendon tear had a significantly longer duration of lymphedema [21]. After breast cancer treatment the lymphatic drainage of the muscle could be affected [17]. We aimed to detect the possible effects of BCRL on the muscle stiffness. The biceps muscle was chosen for this goal because it was relatively superficially located and less affected from the underlying bone artefacts. This is the first study in the literature assessing the stiffness of biceps muscle among the patients with BCRL.

Volumetric and circumferential measurement methods are commonly used to monitor lymphedema [22]. However, the early stage of lymphedema may exist months or years before swelling occurs [23-25]. Previously, minimal limb volume change has been shown to have a significant impact on breast cancer survivors [26]. New assessment tools are needed to early diagnose the lymphedema before swelling of the limb. SWE may provide additional quantitative information in early diagnosis of lymphedema. Further studies are needed to determine SWE's reliability, sensitivity, and specificity in early diagnose of lymphedema.

The patients were over-weighted in our study population. We proposed that obesity could be a factor increasing the predisposition to lymphedema. Our results corresponded with a recent study that showed a significant correlation with increased arm edema and abdominal obesity among the patient with BCRL. Increased BMI should be considered as an aggravating factor for lymphedema severity [27]. Overweight and obese women with BCRL are more likely to have increased abdominal fat than the general population and obesity has been already defined as an increased risk factor for the development of BCRL [28, 29].Water displacement method has been considered to be the "gold standard" for measuring the lymphedema [30]. Considering the difficulties associated with water displacement volumetric method, an alternative method is needed. SWE could be a fast and practical alternative method.

Our study showed that the stiffness of the biceps muscle increases as the severity of lymphedema increases. The main factor increasing the muscle stiffness in severe lymphedema could be the increased pressure among the soft tissues. This pressure may result with compression to the muscles. Histologically, compression may cause acutely edema but chronic compression may progress to fibrosis. SWE results may reflect the structural changes in muscles.

Although swelling and increased volume of the upper limb are the main complaints of women with BCRL, pain and firmness are the other subjective findings [31]. The goal of the treatment modalities in BCRL includes decreasing not only the amount of swelling in the upper limb, but also reducing the pain and firmness. We suggest that SWE could be an objective modality also in monitoring the patients with lymphedema.

A potential limitation of our study was not calculating intra- and inter-rater reliability of the measurements. Other limitation of our study was that the stiffness of the contralateral biceps muscle was not measured. At the beginning of the study, we hypothesized only evaluating the affected extremity. However, it would be better to compare the stiffness of the biceps muscle on the affected and unaffected extremities. The detailed data about TNM stage, radiotherapy protocols with regard to the dose, area and duration could not be collected for all patients. This would be a potential limitation of our study.

In conclusion, BCRL is a chronic and debilitating disease and it might be generally under-diagnosed and undertreated. The effects of lymphedema on a patient's quality of life can be devastating. In conclusion, we suggest that the biceps muscle stiffness measured by SWE could provide a quantitative tool in early detection of lymphedema and might be helpful in objective monitoring lymphedema during follow-up in patients with BCRL.

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