Lymphology 50 (2017) 84-94

IS ULTRASONOGRAPHY A USEFUL METHOD TO EVALUATE THE EFFECTIVENESS OF COMPLEX DECONGESTIVE THERAPY IN BREAST CANCER-RELATED LYMPHEDEMA?

D. Sezgin Ozcan, O. Oken, M. Dalyan Aras, B.F. Koseoglu

Department of Physical Medicine and Rehabilitation (DSO,MDA,BFK), Ankara Physical Medicine and Rehabilitation Training and Research Hospital, and Department of Physical Medicine and Rehabilitation (OO), Liv Hospital Ankara, Ankara, Turkey

ABSTRACT

In recent years the use of ultrasonography has become widespread in the field of lymphedema especially as an aid for diagnosis. The aim of this study was to evaluate whether ultrasonography is a useful method to assess the efficacy of complex decongestive therapy (CDT). Circumferences and ultrasonographic evaluations (cutis and subcutis thickness) were performed at 10 cm proximal and distal to the elbow and limb volume (upper and forearm) was calculated from circumferences at six anatomic landmarks by using truncated cone formula. Measurements were recorded before and after CDT on both sides. A total of twenty-six women (mean age 51.3 ± 10.8) with the diagnosis of breast cancer-related lymphedema (BCRL) were enrolled in the study. Significant reduction in the subcutis thickness was observed on the affected side after the treatment period, and the percentage change in subcutis thickness was correlated with the percentage change in edema. This study also demonstrated that the soft tissue thickness was higher in the affected arm and ultrasonographic findings were consistent with the other measurement methods (circumferences and limb volumes). Considering that ultrasound imaging is patient-friendly, non-invasive, and cost-effective, we recommend its more widespread use for evaluating treatment efficacy in BCRL.

Keywords: complete decongestive therapy, postmastectomy lymphedema, treatment efficacy, ultrasound

Lymphedema is a disorder characterized by the accumulation of protein-rich lymphatic fluid in the cutaneous and subcutaneous tissue. It is divided into primary and secondary lymphedema based on the underlying cause. Primary lymphedema develops due to the congenital abnormalities while secondary lymphedema is an acquired disorder resulting from alteration of lymphatic vessels or lymph nodes. Common causes of secondary lymphedema are cancer and its treatment (surgery, radiation therapy), trauma, tumor, burn, and inflammation (1-4). Upper extremity lymphedema develops in breast cancer survivors. The related risk factors include the number of removed axillary nodes, radiotherapy, presence of postoperative axillary hematoma, seroma, or infection, overweight and reduced physical activity (5,6). Its prevalence ranges from 10-35% after breast cancer treatment and results in a reduction in level of physical activities and functions, psychological problems, and reduced health-related quality of life (1,5,7). Although there

is no cure for this condition, early diagnosis and initiation of treatment are required to provide optimal benefits (1,8). Lymphedema is defined based on clinical findings in patients with known risk factors, and when needed, specialized diagnostic tests are performed including volumetric measurement, soft tissue and lymphatic vessel imaging (9). The patient's subjective complaints such as perceived swelling and the sensation of heaviness or tightness are also important and require careful follow-up (10).

In lymphedema, high protein content of the lymphatic fluid in the interstitial space increases the limb volume and activates neutrophils, macrophages, and fibroblasts leading to tissue fibrosclerosis. Observing the presence of these histological changes is important for estimating the prognosis and response to the lymphedema treatment (2,11). Volumetric and circumferential measurements are the widely used methods for the detection and follow-up evaluation of lymphedema but they can't evaluate the histological properties. The other less common methods are the bioelectric impedance used for early detection of the lymphedema and tonometry for assessment of elasticity. Only magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography (US) can be used in both diagnosis and evaluation of the histological characteristics of the affected soft tissues (12-15). Considering the cost, ease of use, and patient-friendly properties, ultrasonography seems to be more advantageous than CT and MRI for lymphedema patients. Ultrasonography is a reliable and valid method to evaluate the thickness of the cutaneous and subcutaneous compartments and fibrotic changes in the subcutaneous tissue in lymphedema patients (12,16,17). In recent years, the use of ultrasonography has become widespread in the field of lymphedema especially in diagnosis and evaluation of elastic properties of the tissue, but not commonly in the follow-up evaluation including treatment efficacy.

Complete decongestive therapy (CDT) is a multicomponent therapeutic approach accepted as a standard treatment of lymphedema. It consists of manual lymphatic drainage (MLD), compression therapy, therapeutic exercises, skin care, and patient education. The aims of the CDT are to reduce the extremity volume by moving lymph fluid from affected lymphotomes using residual lymphatics, reduce fibrotic tissue, and avoid the development of complications and recurrences. In the literature, multiple studies have demonstrated that CDT is an effective treatment method for reducing limb volume and severity of pain and in improving the quality of life in patients with breast cancer-related lymphedema (9,15,18-20). Volumetric and circumferential measurements are mostly used to evaluate the efficacy of CDT but recently it has been considered that US may also be a practical and sensitive method for assessment of the CDT response (2).

Most studies in the literature related to ultrasonographic evaluation in lymphedema are based on use for diagnosis. In these studies, it has been shown that the cutis and the subcutis thickness were increased in the affected arm compared to the contralateral arm (3,12,14,21,22). The few studies which used ultrasonography for evaluation of the effectiveness of CDT only showed reduction in the cutis and subcutis thickness without any comparisons with the other measurement methods (2,7). In this study, we evaluated the influence of complex decongestive therapy on the soft tissue thickness and the consistency of the changes in ultrasonographic findings along with the circumferential measurement and the limb volume in patients with breast cancer-related lymphedema.

MATERIALS AND METHODS

Subjects

A total of 45 consecutive women with the diagnosis of breast cancer-related lymphedema (BCRL) were evaluated in the lymphedema clinic at the Ankara Physical

Medicine and Rehabilitation Training and Research Hospital from April to November 2013. A difference of 2 cm or more in circumferential measurements between the affected and unaffected arms after the breast cancer treatment was accepted as sufficient for BCRL diagnosis. Subjects with unilateral stage 2 BCRL (9,23) and who were at least three months post breast-cancer treatments were eligible for the study. Subjects with recurrence or metastasis of breast cancer, edema due to other reasons (heart, kidney or liver diseases, primary lymphedema, filariasis), or who had contraindications for application of CDT (active infection, deep vein thrombosis/thrombophlebitis, cardiac edema, peripheral artery disease) were excluded. Considering previous medical history and physical examination findings, we enrolled only 28 of 45 potential patients in the study (eight patients had stage 1 and four patients had stage 3 lymphedema; three patients had metastatic disease, and two patients had cellulitis on the affected arm). During the treatment period, one subject developed cellulitis and one subject was diagnosed with recurrence of ipsilateral breast cancer. Therefore, two subjects were dropped from the study. In total, 26 subjects completed the treatment and were included the final analysis. Approval was obtained from the hospital Ethics Committee, and all participants provided written informed consent.

Treatment Protocol

All subjects underwent CDT phase 1 program including MLD, compression bandages, remedial exercises, and skin care. MLD was applied by a physiotherapist qualified in the Vodder method five times a week for three weeks (a total of 15, 45 minute sessions). MLD was followed by daily multi-layered short-stretch bandaging worn for 21-24 hours a day. Abdominal breathing exercise and remedial exercises were performed with the bandages on. Subjects were given advice on skin and nail care.

Assessment and Outcome Measures

Baseline socio-demographic and clinical properties were recorded for each patient. The circumferential measurements, ultrasonographic measurements of soft tissue thickness, and volumes of upper limbs were recorded before and after CDT on both sides. Interlimb differences of volumes, circumference, and soft tissue thickness were used to evaluate the consistency of these three measurement methods. The percentage change in edema and percentage change in subcutis thickness were also calculated separately for upper and forearm to evaluate the effectiveness of the CDT and the correlation between the two assessment methods.

Circumferential Measurements

The circumferential measurements (cm) were taken horizontally at five anatomic landmarks: the wrist, 10 cm below elbow, elbow, 10 cm above elbow, and axilla by a plastic tape using a slight pressure. The upper limb was divided into four segments by the mentioned anatomic landmarks, and arm volume was calculated using a formula for truncated cone. The sum of these volumes gives the total volume of the limb (24). Limb volume was calculated as two separate segments (upper arm and forearm) (cm^3) for both affected and unaffected sides. Percentage change in edema was calculated using the following formula: Percentage change in edema = (Vi - Vf)/(Vi - Vn) x 100 (Vi: the initial volume of the lymphoedematous limb, Vf: the final volume of the lymphoedematous limb, Vn: volume of the normal limb). The circumferences of 10 cm proximal and distal of the elbow crease were recorded before and after the therapy on both sides and the correlations were evaluated with the soft tissue thickness at the same landmarks.

Ultrasonographic Measurement

Ultrasonography was performed by using

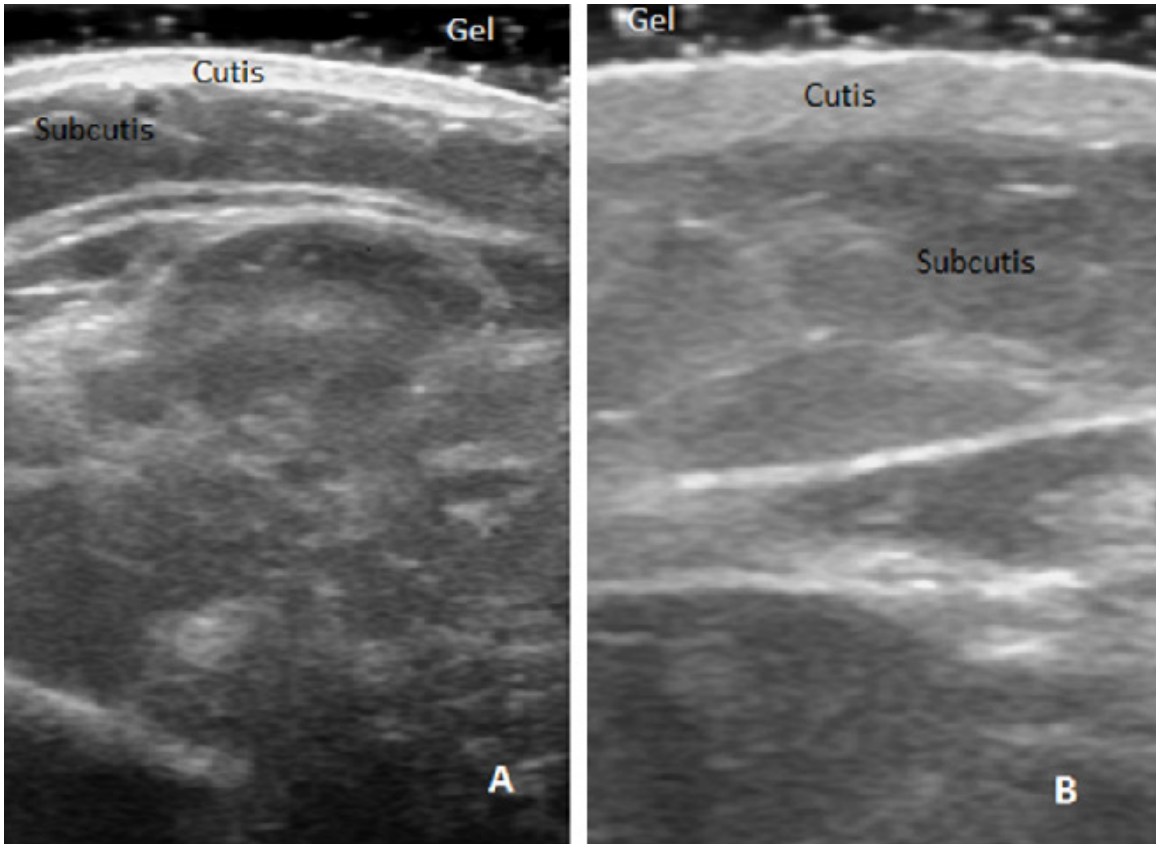

Fig. 1: Ultrasonographic images of a patient with unilateral breast cancer-related lymphedema demonstrating cutaneous and subcutaneous thickness A: Unaffected arm B: Affected arm with increased cutis and subcutis thickness.

a linear array probe (7-12 MHz Logiq P5; GE Medical Systems, Wisconsin, USA). To reduce inter-operator error, the same physiatrist experienced in neuromuscular ultra-sound performed the measurements. During each measurement, patients were seated with their forearm supinated and extended on a pillow. The ultrasound gel was applied to the skin liberally and the probe placed perpendicular to the skin surface. The position of the probe was vertical to the arm axis. No pressure was applied to the probe to avoid affecting the soft tissue thickness. The ultrasound image was obtained when the thickness of the gel layer was at least 1 cm and the cutis and the subcutis layers were clearly distinguishable. The measurements were done at the following sites: 1) 10 cm proximal to the elbow crease along the line parallel to arm axis from the midpoint of the medial and lateral epicondyles and 2) 10 cm distal to the elbow crease along the line parallel to arm axis from the midpoint of the medial and lateral epicondyles. Ultrasonographic images were taken three times at each landmark, and mean results were calculated. The cutis (epidermis and dermis) thickness (between entry echo under the gel layer and the dermis-subcutaneous boundary) and the subcutis thickness (between the cutis-subcutis and the subcutis-muscle boundary) (mm) were measured (*Fig. 1*). These measurements were performed before and after CDT for both sides.

TABLE 1
Socio-Demographic and Clinical Characteristics of Subjects

Variables	N=26
Age (years	51.3 ± 10.8
BMI (kg/m^2)	30.24 ± 4.66
Education level, low/high	6/10 (61.5/38.5)
Work status, employed/non-employed	22/4 (84.6/15.4)
Marital status, married/single	21/5 (80.8/19.2)
Time since cancer diagnosed (months)	62.19 ± 63.57
Duration of lymphedema (months)	25.5 ± 27.67
Side of lymphedema, right/left	13/13 (50/50)
History of radiation therapy	21 (80.8)
History of chemotherapy	25 (96.2)
Type of operation	
Lumpectomy+LND	2 (7.7)
Radical mastectomy+LND	1 (3.8)
Modified radical mastectomy+LND	22 (84.6)
Breast conserving surgery+LND	1 (3.8)
Presence of lymph node metastasis	20 (76.9)

Values are mean ± SD and n (%). BMI= body mass index.
LDN= lymph node dissection

Percentage change in subcutis thickness was calculated using a corresponding formula to that used for percentage change in edema (above) to assess the effectiveness of CDT.

Statistical Analysis

Statistical analysis was performed using SPSS software package (version 20.0, SPSS Inc., Chicago, IL). Distributions of continuous variables were evaluated by Shapiro-Wilk test. Descriptive statistics were expressed as mean ± standard deviation for continuous variables, median (minimum-maximum) for discrete variables and number (n) and percentage (%) for categorical variables. The significances of the difference in median values between the affected and unaffected arms were analyzed with the Mann-Whitney U test. The Wilcoxon test was applied to determine significant changes between before and after CDT. Spearman correlation analysis was performed to evaluate the consistency of the measurement methods. A p value of <0.05 was considered significant.

RESULTS

A total of 26 female subjects (mean age 51.3 ± 10.8) with the diagnosis of BCRL completed the treatment period. Two subjects had ductal carcinoma in situ and 24 of 26 subjects had invasive ductal carcinoma. *Table 1* displays the socio-demographic and clinical properties of the subjects.

Pre-treatment comparisons between affected and unaffected arms revealed significantly high values of limb volume, circumference, and soft tissue thickness (cutis and subcutis) in both upper and forearm on the affected side ($p<0.01$) *(Table 2)*. Following completion of the CDT program, limb volume, circumference, and subcutis thickness were decreased signifi-cantly on the affected side ($p<0.001$). But no statically significant change was observed in the cutis thickness ($p>0.05$) (*Tables 3 and 4*).

Consistency between findings of ultrasonographic and circumferential measurements was assessed on the affected side before and after the therapy. Significant correlations of the interlimb difference of subcutis thickness with the interlimb difference of circumferences and limb volumes were revealed (*Table 5*). After treatment,

TABLE 2
Pre-Treatment Comparisons of Volumes, Circumferences, and Soft Tissue Thickness Values in Affected and Unaffected Sides

	Affected side	Unaffected side	p
Volume (cm^3)			
upper arm	1767.52 (1122.08-2625.66)	1387.20 (1040.34-2380.57)	0.005
forearm	1046.84 (768.17-1675.62)	878.38 (629.90-1217.68)	0.001
Circumference (cm)			
10 cm proximal to elbow	34.0 (25.5-41.5)	29.0 (25.0-40.0)	0.001
10 cm distal to elbow	26.75 (22.0-35.0)	24.0 (20.5-31.0)	0.002
Soft tissue thickness (mm)			
10 cm proximal to elbow			
cutis	2.08 (1.36-3.08)	1.54 (0.72-2.62)	<0.001
subcutis	9.37 (4.26-20.29)	6.20 (2.5-19.12)	0.001
10 cm distal to elbow			
cutis	2.35 (1.27-3.80)	1.63 (1.27-2.17)	< 0.001
subcutis	8.78 (4.10-16.57)	5.55 (2.48-14.86)	<0.001

Note: Values are median (minimum-maximum). Significance at $p<0.05$

TABLE 3
Comparisons of Volumes and Circumferences Before and After CDT in Both Affected and Unaffected Sides

	Pre-treatment	Post-treatment	P value
Circumference (cm)			
Affected side			
10 cm proximal to elbow	34 (25.5-41.5)	32.75 (24.5-40.5)	<0.001
10 cm distal to elbow	26.75 (22-35)	25.5 (20.5-33)	0.001
Unaffected side			
10 cm proximal to elbow	29 (25-40)	29 (25-38.8)	0.66
10 cm distal to elbow	24 (20.5-31)	24 (20.3-31)	0.35
Volume (cm^3)			
Affected side	1767.52 (1122.1-2625.7)	1619.69 (1018.8-2449.6)	<0.001
upper arm	1046.84 (768.2-1675.6)	920.1 (704.9-1493.7)	<0.001
forearm			
Unaffected side	1387.20 (1040.3-2380.6)	1380.4 (1030-2364)	0.42
upper arm	878.38 (629.9-1217.7)	868.6 (634.6-1220.8)	0.12
forearm			

NOTE. Values are median (minimum- maximum). Significance at $p<0.05$

the mean percentage change in edema in the upper and forearm were 36.9% and 40.3% and the mean percentage change in subcutis thickness in the upper and forearm were 34.6% and 37.5%. These were correlated in both upper and forearm on the affected side (respectively r=0.530 p= 0.013 and r=0.605 p= 0.006).

TABLE 4
Comparisons of Soft Tissue Thickness Before and After CDT in Both Affected and Unaffected Sides

Variables	Pre-treatment	Post-treatment	P value
Affected side			
10 cm proximal to elbow			
cutis thickness	2.08 (1.36-3.08)	2.02 (1.44-3.62)	0.43
subcutis thickness	9.37 (4.26-20.29)	7.82 (4.05-19.50)	<0.001
10 cm distal to elbow			
cutis thickness	2.35 (1.27-3.80)	2.17 (1.3-3.28)	0.14
subcutis thickness	8.78 (4.10-16.57)	7.10 (4.07-15.20)	<0.001
Non-affected side			
10 cm proximal to elbow			
cutis thickness	1.54 (0.72-2.62)	1.52 (0.69-2.58)	0.24
subcutis thickness	6.20 (2.5-19.12)	6.18 (2.9-19.08)	0.32
10 cm distal to elbow			
cutis thickness	1.63 (1.27-2.17)	1.64 (1.20-2.15)	0.34
subcutis thickness	5.55 (2.48-14.86)	5.52 (2.40-15.02)	0.13

NOTE. Values are median (minimum- maximum). Significance at p<0.05

TABLE 5
Correlations of the Absolute Subcutis Thickness with the Absolute Circumferences and Volumes in Upper And Forearm Before and After the CDT]

	Pre-treatment		Post-treatment	
	r	p value	r	p value
Upper arm				
Interlimb difference of	0.55	0.003	0.71	<0.001
circumference	0.57	0.005	0.58	0.008
Interlimb difference of volume				
Forearm	0.54	0.004	0.54	0.004
Interlimb difference of circumference	0.57	0.005	0.58	0.009
Interlimb difference of volume				

Values are median (minimum-maximum). Significance at p<0.05

DISCUSSION

Breast cancer-related lymphedema is usually not a life-threatening condition but causes several psychosocial problems and limitations in physical functions leading to reduced health-related quality of life. In recent years, use of ultrasonography has become widespread in the field of lymphedema for diagnosis and evaluation of soft tissue structures but use for examining response to treatment has not been widespread. The aim of this study was to evaluate whether ultrasonography is a useful method to assess the efficacy of CDT. In this study, significant reduction in the subcutis thickness was observed on the affected side after the treatment period, and the percentage change in subcutis thickness was correlated with the percentage change in edema. This study also

demonstrated that the soft tissue (skin and subcutis) thickness was higher in the affected arm, and ultrasonographic findings were consistent with measurements of circumferences and limb volume in both the upper and forearm.

In lymphedema, increase in protein and cell debris components stimulate the activities of neutrophils, macrophages, and fibroblasts, and cause swelling of the affected extremity. If left untreated, lymphedema leads to chronic inflammation which stimulates fibrosis and in advance stages, keratosis and skin papilloma (11,25). The most common measurement methods in use for diagnosis and follow-up are circumferential and volumetric evaluation. But these methods can't give information about the structure of soft tissue as CT, MR, and US. These methods may provide information for prediction of treatment efficacy and prognosis but both CT and MRI are expensive, time-consuming, and CT has the added risk of radiation exposure (2). Ultrasonography is a patient-friendly, easy-to-use, time and cost effective measurement method providing the knowledge of soft tissue structure and may be a useful method for all diagnosis, assessment, and prediction of the treatment efficacy.

Ultrasonographic evaluation of lymphedematous tissues reveals different patterns of ultrasonographic findings caused by morphological alterations in the dermal and subdermal layers. In lymphedema, the dermis shows homogenous hypo-echogenic changes because of water accumulation in the collagen tissue. The subcutaneous tissue shows different patterns of echographic findings with the first pattern showing more uniform hypo-echogenic reflection because of the diffuse accumulation of protein-rich lymphatic fluid that is seen more frequently in acute lymphedema. The second pattern is hyperechogenic areas surrounded by hypo-echogenic traces due to the adipose tissue surrounded by a fluid with fibrous tissue. The third pattern is homogenous hyperechogenic appearance due to the overgrowth of adipose tissue which is observed in patients with chronic edema (21). Several predictive factors of the response to the treatment were suggested. The presence of lymph fluid spread into the extracellular matrix of the subcutaneous layer was proposed as a factor of better response while the presence of fibrosis with the formation of adipose tissue and presence of less water would lead to lower treatment efficacy (21,26). In this study, we didn't evaluate the histological properties and the relation with the responses to the treatment. We only evaluated the cutis and subcutis thickness by ultrasonography.

In the literature, several studies have shown that the cutis and the subcutis thickness were higher in the affected arm than the contralateral arm (3,12,14,21,22). Mellor et al also suggested that evaluating the skin thickness by ultrasonography may be useful for diagnosing lymphedema because of the uniform increase all around the arm while subcutis swelling varies (14). In our study, we found that both the cutis and the subcutis thickness were increased on the affected side, compatible with the previous studies. Because lymphedema mostly affects the distal upper arm and proximal forearm, we used 10 cm above and below of the elbow as the anatomic landmarks. But for ease of the application, we only used the ventral side of the arm for assessment. In contrast to these studies, we also evaluated the consistency of subcutis thickness measurement with circumferences and limb volumes (separately for upper and forearm), and significant correlations were found with these commonly used methods. In the literature, a few studies have compared these measurement methods for consistency. The study by Uzkeser et al demonstrated significant correlation of dermal thickness with the water immersion method and circumferences only in the forearm region but they didn't evaluate the correlations of subcutis thickness. Considering that the subcutaneous tissue contributes more to arm volume in lymphedema, we preferred to analyze the correlations based on subcutis

thickness. The results of our study support the use of ultrasonography in the diagnosis of lymphedema as a method consistent with limb volumes and circumferences.

Complex Decongestive Therapy (CDT), the mainstay therapy of lymphedema, consists of two phases, and this study only evaluated the short-term effect of the first intensive phase on lymphedema volume. Manual Lymph Drainage (MLD) is the main component of CDT and involves specific hand movements stimulating excess interstitial lymph fluid from congested areas among damaged lymphatics into the residual functional lymph vessels and nodes. Compression bandages applying after MLD creates an internal pump-like action between the rest and action of muscles leading to movement of the lymph fluid from the congested areas into the blood vascular circulation. Bandages also prevent re-accumulation of lymph fluid and help to maintain volume reduction after MLD. MLD and compression bandages also provide reduction and breaking up fibrosis of in the tissues (9). Assessment of treatment efficacy is mostly performed by comparing the measured circumferences and limb volume before and after the therapy but, in recent years, interest in the use of ultrasonography for this purpose has increased.

In the literature, we found a few studies using ultrasonography for the evaluation of the effects of CDT in breast cancer-related lymphedema. These studies only showed the reduction in the cutis and subcutis thickness in the post-treatment evaluations without any comparisons with the other measurement methods as we did. Lee et al demonstrated that after a two-week CDT program that soft tissue thickness was significantly reduced only at the elbow and 10 cm above the elbow but not at 10 cm below the elbow while the circumferential measurements revealed a significant reduction in all three points (2). A second study by Ranheer et al after a CDT program demonstrated a significant reduction in both cutis and subcutis thickness of the edematous limb (7). A study by Uzkeser et al evaluated the effectiveness of MLD and intermittent pneumatic compression pumping in lymphedema treatment and found a significant decrease in dermal thickness after both treatments but they didn't evaluate the changes in subcutis thickness (27). Our results showed disparity from the mentioned studies because we found significant decrease only in subcutis thickness not in cutis thickness. Previously it has been suggested that the increase in subcutaneous tissue contributes most to the lymphedema volume (21). Therefore, a decrease in subcutis thickness instead of cutis thickness after volume reduction by CDT can be explained by the light of this information. Different from previous studies, we also evaluated consistency of the percentage change in subcutis thickness (10 cm above and below the elbow) compared with percentage change in edema reduction (upper and forearm) and found a significant correlation between the two assessment methods. Percentage change in edema reduction is a widely used and important determiner in the assessment of the response to the treatment.

The limitations of this study are the small sample size and not including any long-term follow-up evaluation after the three-week CDT. In addition, only patients with stage 2 lymphedema were enrolled in the study because this group was expected to gain the most benefits from the treatment. Therefore the results can't be generalized to stage 1 or 3 lymphedema patients. The other limitation is that determination of limb volume used a calculated limb volume derived from circumferential measurements instead of the gold standard water immersion method. We preferred to use this method because it is also a reliable and valid method which is more practical than the water immersion method. It has also been demonstrated that these two methods have a strong correlation (28,29).

According to our results, pre- and post-treatment measurement of subcutis thickness

using ultrasonography seems to be a useful method in the assessment of the efficacy of CDT. Moreover, we found that the ultrasonographic measurements correlated with the most commonly used assessment methods of circumferential measurements and limb volume calculated from circumferences. Considering that ultrasound imaging is patient-friendly, non-invasive, and cost-effective, we recommend more widespread use for evaluating treatment efficacy in BCRL. Further long-term studies with greater number of patients including stage 1 and 3 lymphedema are needed.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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Didem Sezgin Ozcan, MD
Ankara Physical Medicine and Rehabilitation Training and Research Hospital
Ankara, Turkey
Tel: +90 (312) 310 32 30
Fax: +90 (312) 311 80 54
E-mail: sezgindidem@gmail.com