Lymphology 44 (2011) 72-81

MEASUREMENT OF LYMPHEDEMA USING ULTRASONOGRAPHY WITH THE COMPRESSION METHOD

C.-Y. Lim, H.G. Seo, K. Kim, S.-G. Chung, K.-S. Seo

Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul, Korea

ABSTRACT

Lymphedema is swelling of soft tissues by accumulation of lymphatic fluid due to failure of the lymphatic drainage system. Although most measures for lymphedema focus on change of volume or size of the extremity, the physical properties of the tissue such as resistance to compression are also of clinical importance because they affect the quality of life of lymphedema patients. In this study, we aimed to compare the thickness and resistance to compression of the skin and subcutis between the affected and unaffected arms of patients with lymphedema by using ultrasonography together with the compression technique, and we also investigated the factors that have an influence on the results. Thirty-nine patients with post-mastectomy lymphedema participated in this study. All ultrasonographically-assessed thicknesses of skin and subcutaneous tissue in affected upper arms and forearms were significantly larger than the contralateral (p<0.05) while all resistances to compression values were significantly lower (p<0.05). These results suggest that measuring the resistance to compression and thickness using the compression method with ultrasonography may be a valuable tool for evaluating lymphedema after breast cancer surgery.

Keywords: lymphedema, resistance to compression, ultrasonography, soft tissue

Lymphedema is a swelling of soft tissue that occurs as a result of the failure of the lymphatic drainage system (1). The accumulation of lymphatic fluid, and often accompanying chronic inflammation of the affected tissue, can further lead to fibrosis and thickening of the subcutaneous tissues (2-3). Lymphedema can be divided into primary (inborn errors) or secondary from obstruction. Secondary lymphedema can be caused by trauma, infection, tumor infiltration, surgical dissection of lymph nodes, or radiation therapy. The majority of cases of secondary lymphedema in the upper extremities develop after surgery for breast cancer (1) with a reported post-mastectomy prevalence ranging from 5% to 60% (4-14). In addition, post-mastectomy lymphedema has a significant impact on the quality of life of cancer survivors (15).

Objective assessment of lymphedema estimates the change in volume and physical properties of affected swollen tissues. Volumes can be measured by volumetry or circumference measurement with using a measuring tape. Volumetry is based on water displacement or optoelectronic estimation (16-19). Optoelectronic volumetry uses the interruption of infrared light beams by the limb that is placed inside a special device with rows of infrared light emitting diodes. It calculates the volume of the limb automatically and accurately (18-19). However, it cannot evaluate tissue changes in lymphedema such as fibrosis. Although tonometry can reveal the change of physical properties of the affected tissue (elasticity), it is not sufficiently reliable (20-24).

Measurement of the change of tissue characteristics is important not only because volumetric change alone cannot signify the severity of lymphedema, but also because the denatured tissue itself can have clinical implications (15). The soft tissue characteristics are significantly associated with the quality of life (QOL) of lymphedema patients. The hard, heavy and tight arm is especially associated with reduced QOL in these patients (25). Magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography have been applied to evaluate the change of subcutaneous tissues in lymphedema patients (22-24). MRI demonstrates a honeycomb pattern within the epifascial compartment along with thickening of the skin and trabecular structures, which suggests dilated collateral lymphatic vessels in the swollen subcutis. However, the cost of MRI impedes its clinical use. CT is useful for monitoring the outcome of decongestive therapy, but it was of limited utility because of radiation exposure (22-24,26-28). In contrast, ultrasonography can be readily applied in an outpatient clinic. It can visualize the thickening of the cutaneous, epifascial and subfascial compartments and the accumulation of interstitial fluid, and it allows for the indirect evaluation of fibrosis (29, 30). In ultrasonography, the hyper-echogenic subcutis can be observed due to interlobular and intralobular water accumulation, increase of adipose tissue, and interlobular and intralobular fibrosis (30-31). Another emerging diagnostic technique for the clinical evaluation of lymphedema is bioelectric impedance. This technique facilitates the noninvasive quantification of extracellular fluid in the extremities (22,32-33), and it is finding increasing application in the early detection and management of lymphedema (34).

In a previous study, we reported that ultrasonography with a compression technique is a reliable method to measure the thickness and "compliance" (or more specifically resistance to compression) of the skin and subcutis of the upper extremity in healthy subjects (35). This parameter is directly related to the hardness of soft tissue in lymphedema.

In this study, we compared the thickness and resistance to compression (RC) of the skin and subcutis between the affected and unaffected arms of patients with post-mastectomy lymphedema by using ultra-sonography together with the compression technique, and we also investigated the factors that influence the results.

METHODS

Study Design

Eligible participants were patients with secondary lymphedema resulting from operation for breast cancer treatment. Lymphedema was confirmed by clinical and lymphscintigraphic examination. For clinical diagnosis, circumference of the affected arm must exceed that of the unaffected arm by two or more centimeters using two points above and below the olecranon or lateral epicondoyle as described by Petrek at al (36). Lymphscintigraphy was used to evaluate the lymphatic drainage in the affected limb, and all patients were confirmed to have an obstructive pattern. Patients were excluded if: 1) the lymphedema was primary, irrespective of the treatment for breast cancer; 2) the swelling was bilateral; or 3) the patients had undergone complex decongestive therapy or other interventions for lymphedema within 3 months.

The study participants were recruited from an outpatient clinic of Seoul National University Hospital, Seoul, Korea. The study protocol was approved by the Institutional Review Board of our hospital. The study was explained to the participants, and written informed consent was obtained from all subjects.

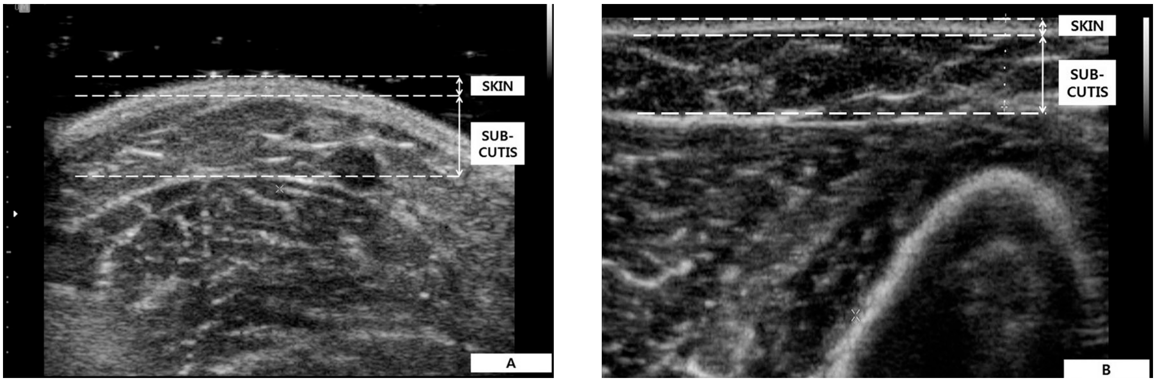

Fig. 1. Ultrasonographic images of the arm of a patient with lymphedema demonstrating the thickness of the skin, subcutaneous tissue, and their sum with minimal compression (A) and with maximal compression (B).

Participants

After being assessed for eligibility and obtaining consents, 39 breast cancer patients participated in this study. The mean age was 57.1±10.2 years (mean ±SD), mean body mass index (BMI) was 24.4±2.8, and mean duration of lymphedema was 31.8±22.1 months. Among 39 patients, 28 (71.8%) were treated by radiotherapy, and 35 (89.7%) were treated by chemotherapy. Twenty-one patients (53.8%) had metastatic tumors, and 18 (46.2%) had lymphedema on the side of their dominant hand. Thirty-seven underwent axillary lymph node dissection while 2 underwent sentinel lymph node resection with modified radical mastectomy. The location of the tumor was the upper outer quadrant of the chest in 24 patients, the upper inner quadrant in 5, the lower outer quadrant in 4, the lower inner quadrant in 1, and the location was not classified in 5.

Outcome Measures

1) Ultrasonographic measurement (35)

The subjects were placed supine on an examination table with the forearm supinated and relaxed. An ultrasound unit (Accuvix V10EX-DOM-00, Medison Co., Seoul, Korea) evaluated the soft tissue on the upper arm and forearm with a 7.5 MHz linear-array transducer. On the upper arm, the transducer was placed 10 centimeter proximal to the elbow crease along the line between the midpoint of the medial and lateral epicondyles of the humerus and the bicipital groove. On the forearm, it was placed 10cm distal from the elbow crease along the line between the midpoint of the medial and lateral epicondyles and the mid-point of radial and ulnar styloid processes.

To measure the thickness of the skin and subcutaneous tissue, an ultrasonographer applied negligible pressure by pasting a sufficient amount of lubricant so that the contour of the tissue beneath a transducer was not distorted (*Fig. 1A*). The images were captured on the upper arm and forearm, and the thickness of the skin, the subcutaneous tissue and their sum were measured by the ultrasound unit. Thickness of the dermis was determined by measuring between the echo entry and the dermis/subcutaneous tissue boundary, and thickness of the subcutaneous tissue was set between the bottom of the dermis and the bright line generated by the fascial connective tissue sheet overlying the muscle (31).

After the thickness was measured, the ultrasonographer applied maximal compression to measure the resistance to compression (RC) of the tissue (*Fig. 1B*). "Maximal compression" was defined as a compression with a sufficient pressure where

TABLE 1
Thickness of Lymphedema and Contralateral Arm Tissues without and with Maximal Compression (n=39)

Region	Compression	Tissue (mm)	Lymphedema (mm)	Contralateral	p value
Upper arm	Without Compression	Skin	1.58 ± 0.61	1.14 ± 0.30	0.000
		Subcutis	9.74 ± 3.45	8.14 ± 2.80	0.010
		Total	11.32 ± 0.69	9.29 ± 0.69	0.002
	With Maximal Compression	Skin	1.12 ± 0.65	0.63 ± 0.20	0.000
		Subcutis	5.37 ± 2.57	3.77 ± 1.29	0.001
		Total	6.49 ± 2.82	4.41 ± 1.30	0.000
Forearm	Without Compression	Skin	1.73 ± 0.69	1.26 ± 0.28	0.000
		Subcutis	9.64 ± 3.54	7.13 ± 2.41	0.001
		Total	11.37 ± 3.78	8.39 ± 2.49	0.000
	With Maximal Compression	Skin	1.36 ± 0.69	0.89 ± 0.30	0.000
		Subcutis	6.38 ± 2.45	4.22 ± 1.47	0.000
		Total	7.74 ± 2.74	5.1 ± 1.53	0.000

additional compression could not produce a noticeable decrease in the thickness of the soft tissue (35).

2) Calculation of resistance to compression

Resistance to compression (RC) is a measurement that indicates the tendency of the tissue to deform from its original configuration as a result of a compressing force. It was calculated with the fractional change in thickness. We defined the RC as the difference between the initial and 'maximal compression' thickness over the initial thickness.

3) Protocols

The thickness and RC were measured in the affected and unaffected upper extremities for each patient. They were assessed for the skin, subcutis and then together, respectively. Those parameters were compared between the affected and contralateral arms.

The circumference was measured by using a measuring tape for the bilateral upper arms and forearms at the same points which were used to measure the thickness with ultrasonographic measurements.

4) Demographic data

The demographic and clinical variables for the patients were analyzed to investigate the factors that influence the ultrasonographic measurements. The demographic variables included the age at study enrollment, body mass index (BMI), and clinical variables including history of radiation therapy or chemotherapy, tumor stage and location, presence of metastasis, dominant side, whether self-decongestive massage was performed, duration of

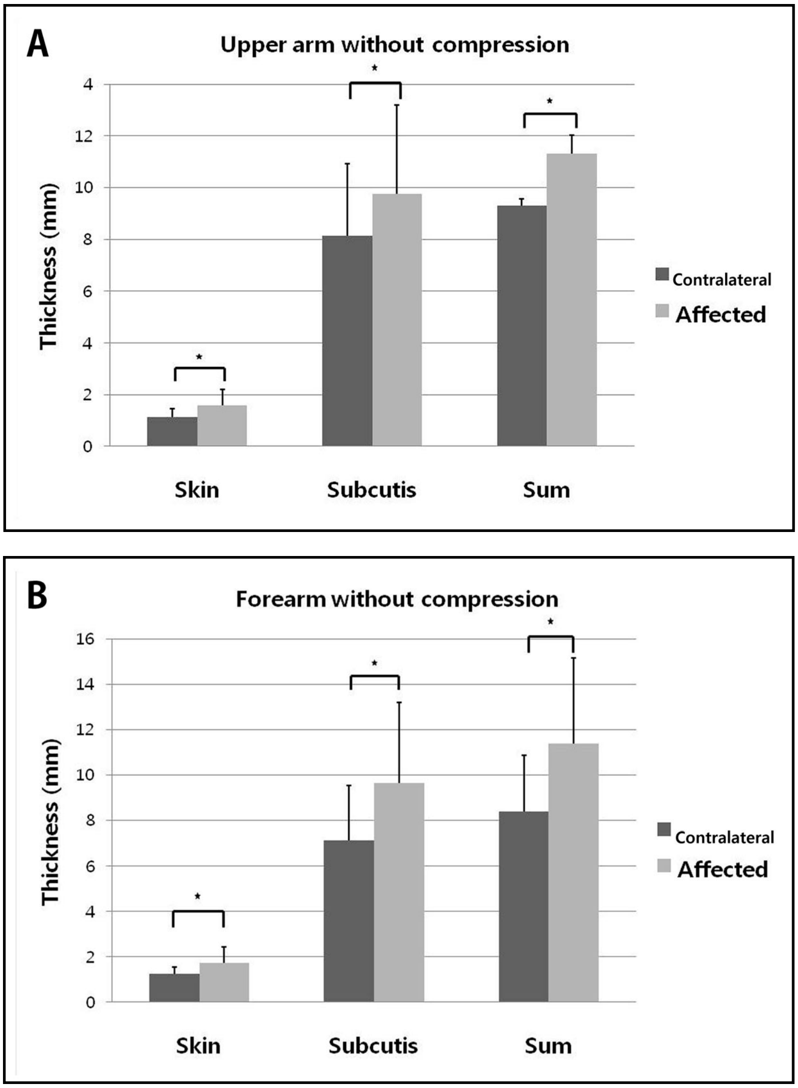

Fig. 2. Thickness of the skin, subcutaneous tissue, and their sum without compression in the affected and contralateral upper arms (A) and forearms (B) (: p-value < 0.05)*

lymphedema, and degree of arm use as represented by a visual analogue scale.

Data Analysis

All the statistical analyses were completed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Thickness and RC were compared between the lymphedematous and contralateral arms by paired t-tests. The influence of the demographic and clinical data on the ultrasonographic measurements was determined using multiple regression analysis and independent t-tests. P-values less than 0.05 were considered statistically significant.

RESULTS

Ultrasonography

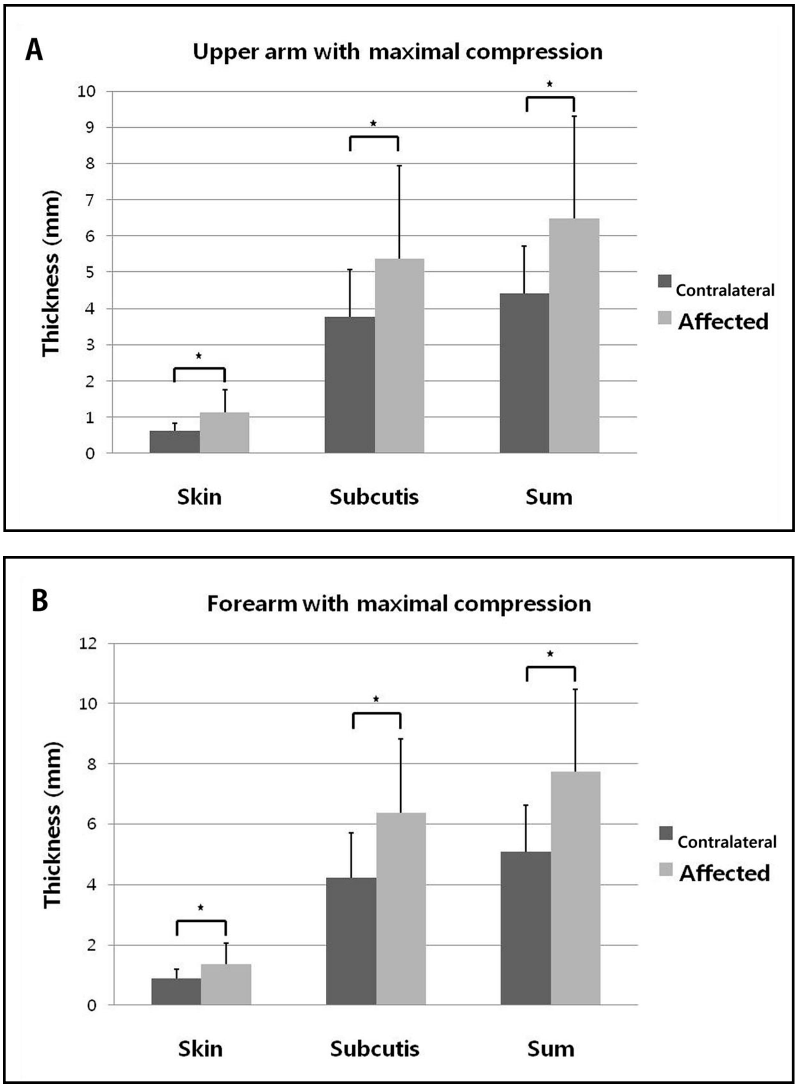

Fig. 3. Thickness of the skin, subcutaneous tissue, and their sum with maximal compression in the affected and contralateral upper arms (A) and forearms (B) (: p-value < 0.05)*

The thickness of the skin, subcutaneous tissue, and their sum (*Table 1*) in the affected upper arm (*Fig. 2A*) and forearm (*Fig. 2B*) without compression were significantly larger compared to contralateral. The values with compression were significantly larger on the affected upper arm (*Fig. 3A*) and forearm (*Fig. 3B*) compared to the contralateral. The RC of the skin, subcutaneous tissue, and their sum in the affected upper arm (*Fig. 4A*) and forearm (*Fig. 4B*) was significantly smaller than the contralateral (*Table 2*).

The Influence of the Demographic and Clinical Data on the RC

Except for BMI, all the demographic and clinical data, including age, body weight, history of radiation therapy or chemotherapy, tumor characteristics and location, metastasis,

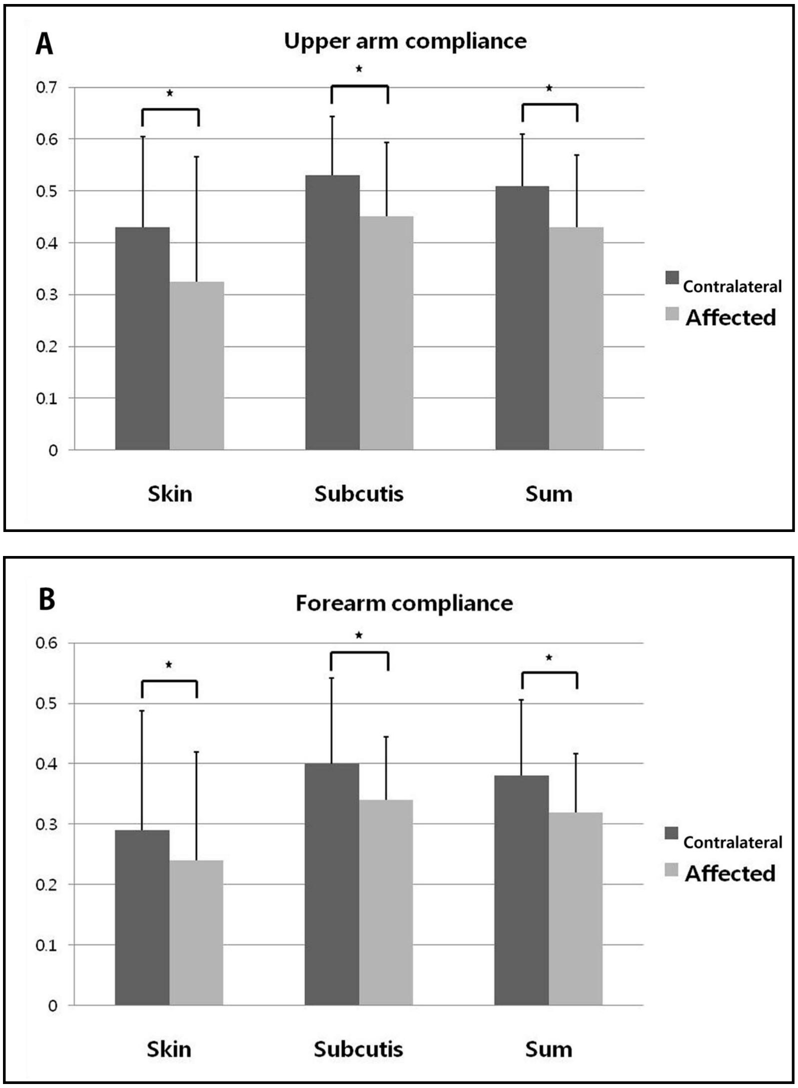

Fig. 4. Compliance of the skin, subcutaneous tissue, and their sum with maximal compression in the affected and contralateral upper arms (A) and forearms (B) (: p- value < 0.05)*

dominant side, whether self decongestive massage was performed, duration of lymphedema and degree of arm use, were not associated with tissue RC by multiple regression analysis or independent t-tests. Only the BMI was significantly correlated with the subcutaneous RC in the affected upper arm (p-value=0.023, R2=0.165).

DISCUSSION

Lymphedema is a dysfunction of lymphatic drainage caused by malformation, damage, or resection of the local lymph nodes (1). The accumulation of interstitial macromolecules elevates the oncotic pressure of the tissue, while the disruption and blockage of lymphatics elevates the hydrostatic pressure within the remaining lymphatics, and both contribute to lymphedema. Stasis of protein-rich fluid with impaired immune clearance in

TABLE 2
Resistance to Compression (RC) in Lymphedema and Contralateral Arms (n = 39)

Region	Tissue	Lymphedema (mm)	Contralateral (mm)	p value
Upper arm	Skin	0.32 ± 0.24	0.43 ± 0.18	0.014
	Subcutis	0.45 ± 0.14	0.53 ± 0.11	0.004
	Total	0.43 ± 0.14	0.51 ± 0.10	0.001
Forearm	Skin	0.24 ± 0.18	0.29 ± 0.20	0.036
	Subcutis	0.34 ± 0.10	0.40 ± 0.14	0.008
	Total	0.32 ± 0.10	0.38 ± 0.13	0.001

the extremity with damaged lymph nodes permits repeated episodes of lymphangitis and cellulitis. Such chronic inflammation leads to further fibrosis and impairment of the affected limb. Fibrosis causes tissue change, which leads to altered physical characteristics of soft tissue such as thickness, elasticity and resistance to compression (2-3).

These study results demonstrate that the thickness of the skin, subcutaneous tissue, and their sum increased in the arms with lymphedema, when estimated by ultrasonography using a no pressure technique. These results are similar to those of a previous study where Mellor et al reported that skin thickness is more closely correlated with arm edema than is the subcutaneous thickness. They suggested that the measurement of skin thickness using ultrasound may be useful clinically for diagnosing lymphedema and can help future investigations of therapeutic techniques (37).

Chronic lymphedema leads to fibrosis, which alters the elasticity and RC of the skin and subcutaneous tissue in lymphedema patients. Fibrosis can be measured by the physical characteristics of the affected region. We previously measured the RC using ultrasonography with the maximal compression technique in healthy people, which had relatively good inter-rater and intrarater reliability (skin, $0.68<ICC<0.81$; subcutaneous tissue $0.85<ICC<0.96$, total tissue, $0.85<ICC<0.97$) (30). This method and parameter is associated with hardness, which is significantly associated with the QOL of lymphedema patients (25). However, this method was not verified on lymphedema patients, and we, therefore, designed this study to examine the usefulness of this method in lymphedema patients. We successfully measured the RCs of the lymphedematous and contralateral arms in the same patient to minimize possible confounding factors.

In our study, almost all the RCs of the skin, subcutaneous tissue, and the total tissue of the affected arm were significantly lower than those of the normal arm using the compression method. This finding indicates that the skin and subcutaneous tissue of the affected arms were stiffer than those of the contralateral arms and further, that this method confirms the feelings of hardness of the affected arm reported by many lymphedema patients. These results are similar to those from a tissue tonometry study of patients with lymphedema (20-21). Therefore, these data indicate that ultrasonography is a useful approach to evaluate the severity of lymphedema because it can quantify the RC, is relatively reliable (35), and is readily available at many outpatient clinics.

In order to explore other confounding factors, we examined the association between these RC and thickness results and clinical and demographic factors that might influence the results. This analysis demonstrated that only BMI was weakly related to the subcutaneous RC of the affected upper arm (R2=0.165), that is, the larger the BMI, the more elastic the subcutis, suggesting that the subcutaneous tissue of the affected upper arm in obese patients might be less stiff than in slender patients.

One limitation of this study is that the RC was calculated with relatively small values, which means that the evaluators need to pay close attention when applying this compression method and using ultrasonography. In other words, the examiners must be properly educated in this method and perform it correctly. Further study is needed to verify the method's validity before it can be widely used and also to assess the relationship between RC and other clinical or therapeutic outcomes of patients with lymphedema.

CONCLUSION

Thickness of the skin and subcutis in the upper arm and forearm was larger and the RC smaller in post-mastectomy lymphedema arms compared to contralateral arms. The thickness and RC were not related to other clinical or demographic factors, except BMI, which was weakly correlated with the RC of the affected upper arm. This study revealed that measurement of RC and thickness using ultrasonography with the compression method is a valuable tool for evaluating lymphedema. We expect that our method could have significant clinical utility because it is reliable and readily available in outpatient clinics.

ACKNOWLEDGMENT

The authors declare that there is no commercial or direct financial interests in the results or support of the research by any authors or organizations/institutions with which the authors are associated.

REFERENCES

1. Warren, AG, H Brorson, LJ Borud, et al: Lymphedema: A comprehensive review. Ann. Plast. Surg. 59 (2007), 464-472.
2. Tiwari, A, KS Cheng, M Button, et al: Differential diagnosis, investigation, and current treatment of lower limb lymphedema. Arch. Surg. 138 (2003), 152-161.
3. Golshan, M, B Smith: Prevention and management of arm lymphedema in the patient with breast cancer. J. Supp. Oncol. 4 (2006), 381-386.
4. Ryan, M, MC Stainton, EK Slaytor, et al: Aetiology and prevalence of lower limb lymphoedema following treatment for gynaecological cancer. Aust. N. Z. J. Obstet. Gynaecol. 43 (2003), 148-151.
5. Querci della Rovere, G, I Ahmad, P Singh, et al: An audit of the incidence of arm lymphoedema after prophylactic level I/II axillary dissection without division of the pectoralis minor muscle. Ann. R. Coll. Surg. Engl. 85 (2003), 158-161.
6. Petrek, JA, RT Senie, M Peters, et al: Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 92 (2001), 1368-1377.
7. Petrek JA, MC Heelan: Incidence of breast carcinoma-related lymphedema. Cancer 83 (1998), 2776-2781.
8. Ozaslan, C, B Kuru: Lymphedema after treatment of breast cancer. Am. J. Surg. 187 (2004), 69-72.
9. Markowski, J, JP Wilcox, PA Helm: Lymphedema incidence after specific postmastectomy therapy. Arch. Phy. Med. Rehab. 62 (1981), 449-452.
10. Hinrichs, CS, NL Watroba, H Rezaishiraz, et al: Lymphedema secondary to postmastectomy radiation: Incidence and risk factors. Ann. Surg. Oncol. 11 (2004), 573-580.
11. Erickson, VS, ML Pearson, PA Ganz, et al: Arm edema in breast cancer patients. J. Nat'l. Cancer Inst. 93 (2001), 96-111.
12. Beesley, V, M Janda, E Eakin, et al: Lymphedema after gynecological cancer treatment: Prevalence, correlates, and supportive care needs. Cancer 107 (2007), 2607-2614.
13. Armer, J, MR Fu, JM Wainstock, et al: Lymphedema following breast cancer treatment, including sentinel lymph node biopsy. Lymphology 37 (2004), 37:73-91.
14. Abu-Rustum, NR, K Alektiar, A Lasonos, et al: The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: A 12-year

experience at Memorial Sloan-Kettering Cancer Center. Gynecol Oncol. 103 (2006), 714-718.
15. Ridner, SH: Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. Support Care Cancer 13 (2005), 904-911.
16. Stanton, AW, C Badger, J Sitzia: Non-invasive assessment of the lymphedematous limb. Lymphology 33 (2000), 122-135.
17. Tomczak, H, W Nyka, P Lass: Lymphoedema: Lymphoscintigraphy versus other diagnostic techniques—a clinician's point of view. Nucl. Med. Rev. Cent. East Eur. 8 (2005), 37-43.
18. Sagen, A, R Karesen, P Skaane, et al: Validity for the simplified water displacement instrument to measure arm lymphedema as a result of breast cancer surgery. Arch. Phy. Med. Rehab. 90 (2009), 803-809.
19. Damstra, RJ, EJ Glazenburg, WC Hop: Validation of the inverse water volumetry method: A new gold standard for arm volume measurements. Breast Cancer Res. Treat. 99 (2006), 267-273.
20. Chen HC, BM Obrien, J Pribaz, et al: The use of tonometry in the assessment of upper extremity lymphoedema. Br. J. Plast. Surg. 41 (1988), 399-402.
21. Chen, YW, HJ Tsai, HC Hung, et al: Reliability study of measurements for lymphedema in breast cancer patients. Am. J. Phys. Med. Rehabil. 87 (2008), 33-38.
22. Rockson, SG: Diagnosis and management of lymphatic vascular disease. J. Am. Coll. Cardiol. 52 (2008), 799-806.
23. Szuba, A, SG Rockson: Lymphedema: Classification, diagnosis and therapy. Vasc. Med. 3 (1998), 145-156.
24. Duewell, S, KD Hagspiel, J Zuber, et al: Swollen lower extremity: Role of MR imaging. Radiology 184 (1992), 227-231.
25. Ridner, SH: Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. Support Care Cancer 13 (2005), 904-911.
26. Filippetti, M, E Santoro, F Graziano, et al: Modern therapeutic approaches to postmastectomy brachial lymphedema. Microsurgery 15 (1994), 604-610.
27. Duewell, S, KD Hagspiel, J Zuber, et al: Swollen lower extremity:Role of MR imaging. Radiology 184 (1992), 227-231.
28. Kibbler, CC, DL Cohen, JK Cruicshank, et al: Use of CAT scanning in the diagnosis and management of hepatic artery aneurysm. Gut 26 (1985), 752-756.
29. Fumiere, E, O Leduc, S Fourcade, et al: MR imaging, proton MR spectroscopy, ultrasonographic, histologic findings in patients with chronic lymphedema. Lymphology 40 (2007), 157-162.
30. Tassenoy, A, J De Mey, T Stadnik, et al: Histological findings compared with magnetic resonance and ultrasonographic imaging in irreversible postmastectomy lymphedema: A case study. Lymphat. Res. Biol. 7 (2009), 145-151.
31. Fumiere, E, O Leduc, S Fourcade, et al: MR imaging, proton MR spectroscopy, ultrasonographic, histologic findings in patients with chronic lymphedema. Lymphology 40 (2007), 157-162.
32. Mayrovitz, HN: Assessing lymphedema by tissue indentation force and local tissue water. Lymphology 42 (2009), 88-98.
33. Mayrovitz, HN: Assessing local tissue edema in postmastectomy lymphedema. Lymphology 40 (2007), 87-94.
34. Ward, LC: Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. Lymphat. Res. Biol. 4 (2006), 51-56.
35. Kim, W, SG Chung, TW Kim, et al:. Measurement of soft tissue compliance with pressure using ultrasonography. Lymphology 41 (2008), 167-177.
36. Petrek, JA, PI Pressman, RA Smith: Lymphedema: Current issues in research and management. CA Cancer J. Clin. 50 (2000), 292-307; quiz 8-11.
37. Mellor, RH, NL Bush, AW Stanton, et al:. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema. Breast J. 10 (2004), 496-503.

Kwan-Sik Seo, MD, PhD
Assistant Professor
Department of Rehabilitation Medicine
Seoul National University Hospital
28, Yeongundong Jongrogu
Seoul, 110-744, Korea
Tel: 82-2-2072-3940
Fax: 82-2-743-7473
e-mail: kurmguro@paran.com