SONOELASTOGRAPHY ORIGINAL ARTICLE

Measurement of Elasticity of Epifascial Tissues in Arm Lymphoedema Using Acoustic Radiation Force Impulse Quantification (ARFI-Q): our experience

A Onorato[1], G Bravo[2], SL Filelfi[1, 3], N Goswami[3]

[1] Linfamed Srl, Udine, Italy

[2] Department of Medicine, University of Udine, Italy

[3] Division of Physiology, Otto Loewi Research Center, Medical University of Graz, Graz, Austria

submitted: Jul 26, 2024, accepted: Aug 24, 2024, EPub Ahead of Print: Aug 26, 2024, published: Aug 31, 2024
Conflict of interest: None

DOI: 10.24019/jtavr.207 - Corresponding author:Dr. Alberto Onorato, a.onorato@linfamed.it

Abstract Aims and objectives: Chronic lymphoedema is associated with fibrosclerosis, lipid cell proliferation, angiogenesis as well as increase of tissue thickness and hardness. Here we quantitively assessed epifascial tissue elasticity in arm lymphoedema patients using the Acoustic Radiation Force Impulse Quantification (ARFI-Q) approach. Materials and methods: Thickness and elasticity of the epifascial tissues of both forearms (healthy and lymphoedematous) were measured, with and without tissue compression, using a Siemens Acuson 2000 - Virtual Touch ultrasound equipment. Differences in ARFI-Q values among epifascial tissue layers (superficial, intermediate and deep) of both forearms were assessed. Quantitative variables were evaluated using Spearman coefficient. ARFI values were evaluated using Kruskal Wallis non parametric test. Results: 41 patients (38 females, 3 males; age 63.3±11 years; weight 72.8±11 kg, height 162.5±7.8cm and BMI 27.6±4.8 kg/m^2) with unilateral breast cancer related lymphoedema were enrolled into this study. The median elastographic values, in m/sec, without compression at the lymphoedematous limb were: superficial layer 1.70 m/s (0.78-2.82); intermediate layer 1.14 m/s (0.71-3.66) and deep layer 2.10 m/s (0.71-4.29). With tissue compression, values were 3.23 m/s (0.98-4.92), 3.16 m/s (1.29-7.92) and 3.65 m/s (1.72-5.70), respectively. In the lymphoedematous limb we found significant differences between intermediate and deep layers with no compression ($p = 0.005$), and between superficial and intermediate layers ($p = 0.004$) as well as intermediate and deep layers ($p < 0.001$) with compression. Conclusions: ARFI Quantification could demonstrate different stiffness values for the three layers in lymphoedematous limbs. The reduced elasticity of deep epifascial tissues could be an expression of fibrotic degeneration. Moreover, elastic compression, normally used as a treatment, could prevent or reduce fibrosis of the more superficial layers.

Keywords Upper limb lymphedema; shear wave elastography; ultrasound imaging; ARFI, fibrosis.

1. Introduction

Lymphoedema is a chronic, progressive disease characterized by the accumulation of protein-rich fluids in the interstitial spaces of the skin and subcutaneous tissues. It is associated with mechanical insufficiency of the lymphatic vascular system[1,2]. Usually, it does not threaten survival, but is accompanied by important consequences, including risk of infections, functional limitations and psychological disorders, with modification of body image, reduction of self-esteem, affective disorders and fear[3,4]. If left untreated, it shows a progressive tissue changes and morphological deformities[5].

Upper limb lymphoedema usually follows axillary lymphadenectomy, which is performed mainly for radical

breast cancer surgery. The prevalence of lymphoedema after breast surgery varies from 10 to 50%, according to Kim et al[6]; the incidence after removal of the sentinel node is only 3%[7].

Chronic stasis of protein-rich fluids in lymphoedema causes inflammation, which leads to an increase in activated fibroblasts, an enhanced production of collagen and the lysis of elastic fibers through the action of different cytokines and chemokines. The consequence is an evolution towards tissue fibrosclerosis. Associated phenomena are a proliferation of lipoid cells and neoangiogenesis: this determines an increase in adipose tissue[8] and can trigger (also for phenomena of local immune depression) the development of angiosarcomas[9].

The assessment of tissue transformations seen in lymphoedema can be inspective and palpatory, with skin showing alterations, ranging from hyperkeratosis to pachydermia (often accompanied by warts and papillomatosis lymphostatica). All these changes can lead to alterations in tissue elasticity.

Instrumental methods that allow the detection of changes in the consistency of lymphoedematous tissues are tonometry and ultrasound. Tonometry provides a quantitative measure of consistency and correlates well with subjective sensation[10]. It further enables a follow-up of tissue changes after conservative treatments[11]. The inability to identify structural changes in the skin and subcutaneous tissue represents a major limitation of this approach[12]. Ultrasound examination allows the study of different features of lymphoedema: presence of fluid accumulation, differences in echogenicity with respect to the healthy segment, changes in the thickness of the dermis and subcutaneous tissue and compressibility of the epifascial tissues.The latter provides numerical data, relating to tissue compressibility (also termed tissue compliance, expressed by the difference of epifascial tissue thickness, after measurement without and then with maximum pressure on the ultrasound probe)[13] and tissue resistance to compression (that is, the ratio between difference of tissue thickness without and with compression, and thickness without compression)[6]. Overall, it refers to the area examined. However, with ultrasound measurements, it is difficult to derive a value of consistency, both in absolute terms and in relation to the compliance of the contralateral, healthy tissues. The development of a particular ultrasound technique, represented by sonoelastography, is relatively recent. This allows to distinguish areas with different consistency, within the examined tissue, with the help of a dedicated software, integrated into the ultrasound equipment. Furthermore, it allows detection of modifications induced by small rhythmic pressures given on the ultrasound probe by the operator, or impressed by vascular pulsation (Strain Elastography - SE), or arising from shear waves induced by the ultrasonic beam (Shear Wave Elastography - SWE)[14,15]. The result can be qualitative (color coded map) or quantitative, with the expression of values in meters/second or KPascal. Sonoelastographic studies, which were initially applied to diagnose liver, breast and thyroid neoplastic lesions, have now other applications. Currently there is a lack of studies that have used sonoelastography for lymphoedema diagnosis and characterization, and most of the previous studies were performed using Strain Elastography. A SWE modality is represented by Acoustic Radiation Force Impulse (ARFI) technique, used to evaluate transversal tissue dislocation generated by ultrasound beam. Data provided can be qualitative (ARFI Imaging), quantitative (ARFI Quantification) or both (ARFI-QI). ARFI Quantification has been used in several studies, as it has been useful in the diagnosis of liver and kidney fibrosis, in particular after organ transplantation[16-20]. The aim of our study was to determine the usability of ARFI Quantification for the characterization of elasticity of epifascial tissues of lymphoedematous arm, and to demonstrate changes in tissue hardness, related to fibrosis. The study has already been published in 2014 in the directory of doctoral dissertations of the University of Udine. It is taken up again for a comparison with subsequent studies related to ARFI sonoelastography applied to lymphedema[21].

2. Materials and Methods

2.1 Study protocol

This cross-sectional study was performed in 2013 at the Lymphological Surgery of Associazione Lotta al Linfedema (Fight Lymphoedema Association), based in Udine. Patients were recruited through telephone invitation or during a medical visit performed by a physiatrist expert for lymphoedema. Included were patients, who had undergone axillary dissection for breast cancer and developed unilateral secondary lymphoedema, with stage II and III lymphoedema (defined as non-pitting irreversible lymphoedema), lasting at least two years. Exclusion criteria that were applied were exclusive distal localization of lymphoedema (wrist and hand); bilaterality of lymphoedema; inflammatory pathology in progress or ended less than one month before; conservative treatment in progress or concluded less than two weeks before; secondary malignant lymphoedema; other dermatological pathology of the upper limbs; pathologies causing anasarca (nephrotic syndrome, severe heart disease, cirrhosis). Informed written consent was obtained from the patients before the study was started. For the research a non-invasive method was used, with application of diagnostic ultrasound, with equipment already approved for human use and regularly marketed for diagnostic purposes.

Data on the medical history of the patients were obtained. Then, the following in-formation was collected: anthropometric data as extent and amount of swelling of the lymphoedematous arm as well as in the healthy forearm (by circumferences measurements and calculation of volumes through mathematical formulas). Patients were then asked to remain in a supine position, with the upper limbs stretched out and with relaxed muscles. The landmarks for instrumental measurements

were then identified and marked with a dermographic pencil. These landmarks were on the right and left forearm, at the union between 1st and 2nd third sections, at the dorsolateral position. Then ultrasound measurement of the epifascial tissue thickness in both, healthy and lymphoedematous forearm, was performed, avoiding any skin compression by using abundant ultrasound gel. ARFI measurement, avoiding skin compression were carried out at different depths of epifascial tissues (superficial level including epidermis and dermis; intermediate level below the dermis and deep level above the muscular fascia). Similarly, ARFI measurements were performed by applying maximum pressure to the probe and therefore to the tissue being examined. Due to the size of the Region of Interest (ROI, that is the portion of tissue where the stiffness is measured) it was not possible to make in all subjects the measurement at the three levels (in particular on the healthy limb). In some cases of lymphoedema it was not possible to differentiate the intermediate level (upper subcutis) from the deep one (deep subcutis): therefore, a single measurement was made for the entire layer. In most cases, only the skin stiffness could be measured on the healthy limb. Ultrasound thickness measurement, without and with maximal compression, was assessed as well. All of these measurements were performed in the same sequence, in order to avoid the influence of tissue modifications, which could affect subsequent assessments. Three measurements were taken for each examined feature. Each ultrasound measurement was performed on a still person, at the end of exhalation. The duration of the visit for each patient was approximately 40 minutes.

2.2. Materials

The Acuson S 2000 device, equipped with the ARFI-Q "Virtual Touch TM" application, for tissue quantification was used to perform the ultrasound measurements. A 14.5 MHz linear probe was used for thickness assessments and a 9 MHz linear probe for ARFI-Q measurements. The data obtained were quantitative, expressed in meters per second. Median values of the measurements were used for statistical analysis.

2.3. Statistical analysis

Descriptive analysis was carried out with the Excel program of the Microsoft Office 2007 application package; the inferential part with statistical software R. Sociodemographic (gender and age) and health-related variables collected from patients' medical history and medical examination, were analyzed using the main statistical indexes (frequencies and mean±SD; median and range for categorical and numerical variables, respectively). The correlation between quantitative variables was evaluated using Spearman coefficient. A comparison between ARFI-Q values obtained in the limb with lymphoedema at different levels (superficial, intermediate and deep) was evaluated using Kruskal Wallis non parametric test (set α=0.05).

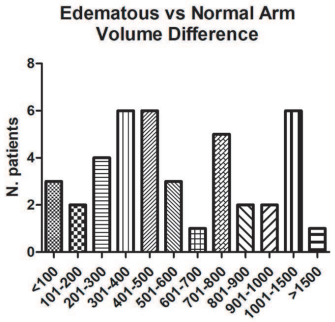

Figure 1 - Volume difference (mL) between lymphoedematous and healthy arms.

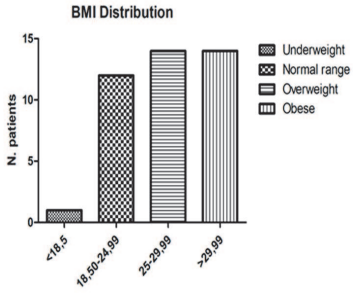

Figure 2 - Distribution of Body Mass Index (BMI).

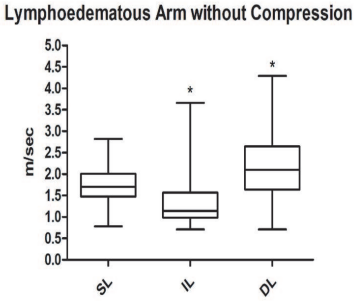

Figure 3 - ARFI measurements without compression at three tissue levels of lymphoedematous forearm (SL= superficial layer, IL = intermediate layer, DL = deep layer). Significant difference between intermediate and deep layer (, p = 0.005).*

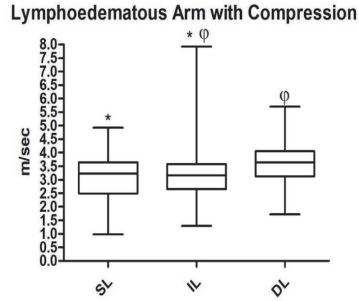

Figure 4 - ARFI measurements with compression at three tissue levels of lymphoedematous forearm (SL= superficial layer, IL = intermediate layer, DL = deep layer). Significant differences between superficial and intermediate level (, p = 0.004) and between inter-mediate and deep layer (φ, p < 0.001).*

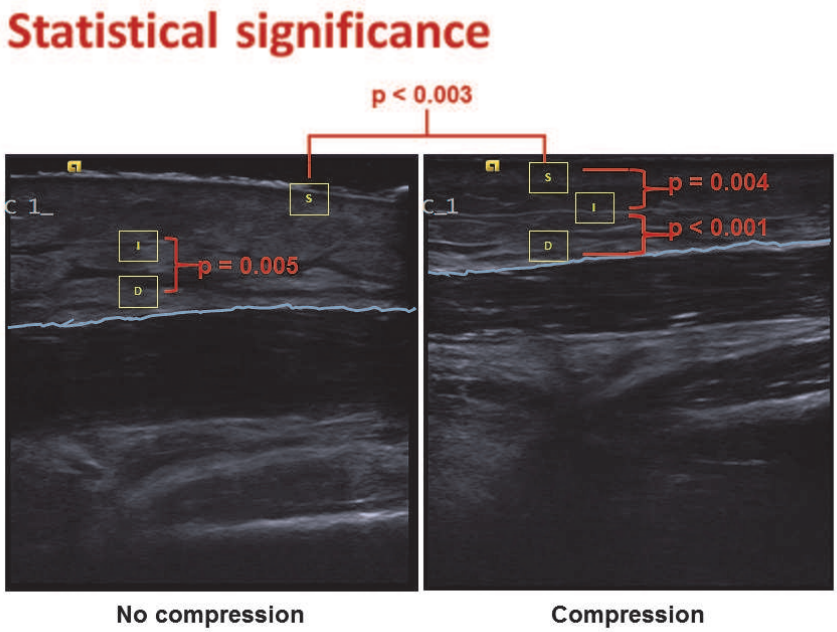

Figure 5 - Statistically significant differences in ARFI measurements between different layers of the lymphedematous limb, without and with compression: between superficial levels (p < 0.003); between intermdiated and deep level without compression (p = 0.005); between superficial and intermediate (p = 0.004) and between intermediate and deep layers (p < 0.001) in measurements with compression.

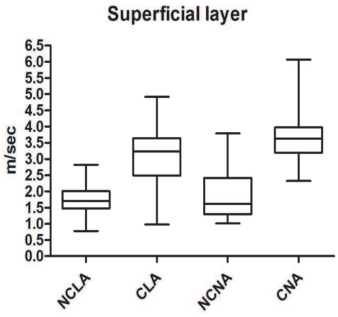

Figure 6 - ARFI measurements at superficial level of both forearms without and with compression: NCLA (no compression lymphoedematous arm) 1.70 m/s (0.78-2.82); CLA (with compression lymphoedematous arm) 3.23 m/s (0.98-4.92); NCNA no compression normal arm) 1.61 m/s (1.01-3.79); CAN (with compression normal arm) 3.63 (2.32-6.07).

3. Results

In total, 41 patients (38 females, 3 males; age 63.3±11 years; weight 72.8±11 kg, height 162.5±7.8 cm, and BMI 27.6±4.8 kg/m^2 participated in this study. The mean duration of lymphoedema was 6±4 years. Arm volume differences between the affected arm and the healthy arm are reported in figure 1.

Out of these patients, 25.4% were overweight and 25.4% were classified as obese (3.6% in class III), as can be seen in figure 2.

In 28 cases, inflammatory episodes were reported (dermatolymphangioadenitis or erysipelas); these inflammatory episodes ranged between 1 to 2 times per year. In 34 cases, periodic combined treatment with manual lymphatic drainage and elastic com-pression bandage was performed. 35 patients used elastic compression garments (25 of them regularly).

3.1. ARFI-Q measurements

At the lymphoedematous limb ARFI measurement without compression (figure 3) gave the following median results: superficial layer 1.70 m/s (0.78-2.82) (number of cases in which it was possible to measure at the layer, n = 41), intermediate layer 1.14 m/s (0.71-3.66) (n=26), deep layer 2.10 m/s (0.71-4.29) (n=35). With maximal compression median results were: superficial layer 3.23 m/s (0.98-4.92) (n=41), intermediate layer 3.16 m/s (1.29-7.92) (n=17) and deep layers 3.65 m/s (1.72-5.70) (n=31) (figure 4). In lymphoedematous limbs significant differences were found between intermediate and deep layers with no compression (p = 0.005) (figure 3), and between superficial and intermediate level (p = 0.004) and intermediate and deep layer (p < 0.001) in the acquisition with compression (figure 5).

At healthy limb ARFI-Q measurement without compression gave the following median values: superficial layer 1.61 m/s (1.01-3.79) (n=41) and deep layer 1.33 m/s (0.79-2.18) (n=14). Applying maximal compression led to median results at superficial level 3.63 m/s (2.32-6.07) (n=41) and at deep layer 3.37 m/s (2.98-3.43) (n=3).

The only completely comparable measurements on both sides and for measure-ments without and with compression are those of the superficial layer (figure 6)

3.2. Ultrasound measurement of epifascial tissue compressibility

Thickness of epifascial tissues (in mm), measured without and with compression on the lymphoedematous and healthy limb are listed in table 1. High correlations were found between the thickness of the epifascial tissue and the changes in compressibility in the lymphoedematous limb (r= 0.921) and in the healthy limb (r= 0.928) (Figure 7 and 8).

	Lymphoedematous forearm without compression (mm)	Lymphoedematous forearm with compression (mm)	Lymphoedematous forearm thickness difference (mm)	Healthy forearm without compression (mm)	Healthy forearm with compression. (mm)	Healthy forearm thickness difference (mm)
Median value	14,55 (6,00-45,50)	8,40 (2,50-16,60)	5,60 (1,20-35,20)	5,95 (1,80-15,80)	3,55 (1,30-7,40)	2,45 (0,00-8,50)

Table I - Median values of epifascial tissue thicknesses (mm) at lymphoedematous and healthy forearms, without and with compression.

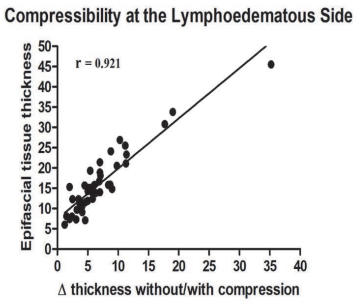

Figure 7 - Correlation between epifascial tissue thickness e and its compressibility at lymphoedematous forearm (r=0,921).

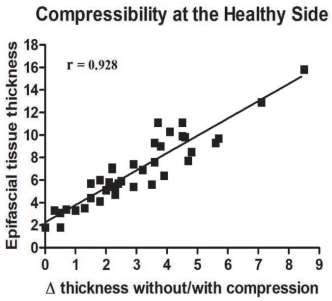

Figure 8 - Correlation between epifascial tissue thickness e and its compressibility at lymphoedematous forearm (r=0,928).

4. Discussion

In our study, ARFI measurements were made on different layers of forearm epifascial tissues: superficial layer, largely corresponding to the epidermis and dermis; intermediate layer, substantially consisting of the upper part of subcutaneous fat; deep layer, corresponding to the whole subcutaneous sector or only to its deep portion, in accordance with the thickness of tissue examined. We found different stiffness values for each layer in lymphoedematous limbs. The reduced elasticity of deep epifascial tissues could be an expression of fibrotic degeneration. Our results, therefore, suggest that the highest values were found at the deep (suprafascial) layer, with levels similar to those of normal kidney and of the 3rd and 4th stages of 4 levels Metavir classification of liver fibrosis[22]. The intermediate values were found at the superficial level, with a measure similar to that of the 2nd-3rdrd Metavir stage. Lowest values were identified at the intermediate (subdermal) tissue layers, corresponding to the 0-1st Metavir stage. The differences detected between the intermediate and deep layers have shown statistical significance, suggesting the possibility that in the deeper layers (in which stagnation of supra-fascial fluid collections is usually more evident) tissue fibrosis develops or is more relevant.

In the assessment of peripheral lymphoedema features, tissue consistency is a poorly evaluated parameter: in the clinical setting, tissue elasticity is usually assessed manually by evaluating the pitting and the liftability of the skin with the pinch test[23, 24]. Conversely, tissue consistency can be an important aspect in monitoring this evolutionary condition, which adds tissue changes to a progressive volume increase. These changes occur as fibrotic, neolipogenetic and neoangiogenetic transformations, of an

entity differing from person to person and, in the same subject, at various body portions and over time. There are some examples of instrumental quantitative estimation of tissue consistency, performed with tonometers and with B-mode ultrasound examination (study of tissue compressibility and compliance)[6, 11, 13]. These methods show certain limitations, mainly the difficulty to adequately measure the hardness of deep integuments. A recent ultrasound diagnostic technique, namely sonoelastography, has emerged as a promising tool in such measurements. It assesses tissue consistency by comparing images, taken before and during small tissue deformations. The two main techniques provide qualitative or semi-quantitative data of tissue elasticity (using SE) or qualitative or quantitative information (using SWE, depending on the modality used)[15].

We used shear wave elastography, in ARFI-Q modality, for this study on forearm epifascial tissue of breast cancer related lymphoedema. We used this approach, as the application of this method in such patients has not been extensively reported. ARFI-Q measurements have previously been used to assess normal and fibrotic liver, spleen, pancreas and kidneys of healthy subjects, in both, adults and children[16-20].

The values for a healthy liver range between 1.25 and 1.60 m/s, whereas in case of fibrosis stiffness can increase to approximately 2.35 m/s (for 4th stage of the Metavir liver fibrosis scale)[22]. In the pancreas, spleen and kidney, normal average values are 1.40m/s, 2.44 m/s and 2.24 m/s, respectively. Maximal compression was applied to the tissue as previously performed by Kim[6]. Using ultrasound, he measured tissue compliance (difference of tissue thickness measured without and with maximum compression exerted with the probe) in lymphedema. Our aim was the reduction of the liquid component: the lymphoedematous tissue reproduces a poroelastic material, in which a solid matrix is permeated by an interconnected network of fluid-filled pores. Compression deforms the matrix, that exhibits elastic properties, while fluid is spatially redistributed over time as response to the squeeze[14]. Compressive elastography was already used to demonstrate spatio-temporal strain responses of edematous tissues, but in a longitudinal manner: color maps of the strain were taken sequentially during a gentle, sustained compression of the tissue[25]. The aim of these studies was to gain a better understanding of the mechanical tissue adaptations rhythmically imposed by the examiner performing SE, and the possibility of distinguishing between normal and lymphoedematous tissues in vivo. Our intention was to exert a maximal, sustained compression in order to highlight the "structural" component of the tissue and therefore reveal or make more appreciable elasticity variations related to the increase in cellularity, collagen fibers and extracellular matrix. As expected, on lymphoedematous forearms we found higher velocities, as a consequence of reduced elasticity. Moreover, median values were more tightly distributed. There was also a maintained gradient between the deep, superficial and intermediate layers, with a statistically significant difference between the superficial and intermediate layers, as well as beetween the intermediate and deep layers.

Our results suggest a difference between the upper and lower subcutaneous layers, probably due to fibrotic alterations of the deep tissue portions in the lymphoedematous forearm. More research is needed in the area of compression measurements, including aspects related to theoretical insights as well as using biomechanical models. Due to their slight thickness, in most cases ARFI measuremens were possible at only one level in the epifascial tissues of the healthy limb, corresponding to the skin and a thin layer of subcutaneous tissue. Only in three healthy limbs, the thickness of the epifascial tissues was sufficient for placement of the ROI at two different depths (skin and subcutaneous layer). Compared to the healthy side, measurements on the lymphoedematous forearm appeared slightly lower without compression and also slightly higher with maximal compression. However, there was no statistical significance in these data. It is possible that the lower hardness at the affected side was related to an increased hydration of the dermis, as is typically seen in lymphoedema.

In recent years, some studies using ARFI-Q on lymphoedema have been published. Chan et al studied 45 patients with lower limb lymphoedema, and 19 patients with upper limb lymphoedema[26]. They compared ARFI-Q measurement of cutis and subcutis with lymphatic obstruction extent, assessed by lymphoscintigraphy. Shear wave speed was significantly higher in limbs with lymphatic obstruction than in limbs without it, at both cutaneous and subcutaneous layers. For affected and healthy limbs, median values of velocities were 2.77 m/sec and 1.74 m/sec, respectively, at cutaneous layer, and 1.90 m/ sec vs. 1.35 m/sec at subcutaneous level[26]. Our results from the lymphoedematous forearm are in contrast with those of Chan et al. at cutaneous layer (1.70 m/sec in our study) and at the subcutaneous tissue layer (1.14 m/sec and 2.10 m/sec). However, in the healthy limbs our observations were similar to those of Chan et al.

Iyigun et al studied with ARFI-Q 36 patients with arm lymphoedema after axillary dissection and radiotherapy[27]. Different values are reported for subcutaneous tissue at different levels of normal and lymphoedematous arm, with median velocity ranging from 1.58 m/sec to 1.6 m/sec; at lymphoedematous forearm median value was 2.09 m/ sec. They found no statistical difference of measures taken at normal and at International Society of Lymphology

(ISL) stage 1 lymphoedema of forearms, while a difference was found between normal and stage 2 lymphoedema of forearms. The reasons for these differences are not easy to understand. Unlike strain elastography, ARFI-Q measurements do not require manual tissue compression and the measurement is conducted automatically[27].This results in better control of force, and therefore the evaluation of deeper structures[12]. Furthermore, Chan and colleagues found that intraobserver reliability of SWE was excellent in the cutaneous tissue and good in the subcutaneous tissue. Interobserver reliability was excellent at both layers. Iyigun et al found similar results[27]. In a recent use of the ARFI-Q to measure stiffness in upper limb lymphedema and in the contralateral healthy limb, values were found that were clearly different from those reported by us and in previously reviewed articles. The values found in the dermis were clearly higher than those in the subcutis, on both sides: in the dermis and subcutis in lymphedema, respectively, 3.054±0.784 and 1.707±0.535 m/sec., and 2.851±0.726 and 1.895±0.603 in the healthy limb. Re-examination after pitting test demonstrated the reduction of stiffness in the dermis, but not in the subcutis[24]. The contrasting results from all these studies could come either from heterogeneous clinical features of patients included in these studies or from portions of subcutaneous tissue examined (superficial, deep or both) and/or type and regularity of application of conservative therapies and use of elastic garments. Moreover, subcutaneous tissue has a different structure, depending on body part assessed. Throughout almost the entire body areolar fat is located between dermis and fascial system, constituted by small fat lobules, tightly packed and vertically oriented. At abdomen, flanks, trochanteric region, internal surface of the upper third of the thigh, knees, and posterior surface of the arm, there is lamellar fat, located under the areolar one, between superficial and muscular fasciae. It is looser than the areolar fat and in obesity it increases in thickness much more than areolar layer[28]. As 25.4% of our patients were overweight and 25.4% were obese (including 3.6% in class III), it is possible that the increase of areolar fat could have led to the greater thickness of the layers measured in our study. Finally, the ARFI measurement sites used in our study could be another factor contributing to the observed differences in elasticity values, in relation to these structural differences of subcutaneous tissues.

Our study allowed also the B-mode ultrasound assessment of compressibility of epifascial forearm tissues, performed on the same location of ARFI quantification. Thickness measurements without and with maximal compression, on both healthy and lymphoedematous limbs, showed a tendency to a greater compressibility on the edematous side compared to the healthy side ($p = 0,0066$). We found a correlation between the thickness values without compression and tissue compressibility (measurement without minus measurement with compression), on both sides. This thickness difference was defined as tissue compliance by Kim et al[6]. This value indicates the tendency of a tissue to deform due to a compressing force and is directly related to the hardness of soft tissue in lymphoedema. In our study consistency of data with sonoelastographic values was not demonstrated. Tissue compliance measurement can be used simply to monitor the progression of lymphoedema over time, as Kim proved the reliability of this evaluation at forearm (excellent) and at upper arm (fair-to-good)[6]. Further studies are necessary to understand the usefulness of these data for assessment of tissue elasticity.

4.1 Limitations

The main limitation of our study is the rarity of reference data related to skin and subcutaneous elastographic measurements, in normal and lymphoedematous limbs. Indeed to date, little literature has been published on the application of elastography to lymphedema. What is currently available does not allow us to fully understand the correlation between the data obtained and the actual tissue phenomena, also because the transformations in case of lymphoedema occur in the direction of fibrosis but also of neolipogenesis. A different case is that of liver disease, where there is a gold standard in tissue assessment, represented by needle biopsy. The large number of ARFI-Q measurements performed and the possibility of their correlation with the bioptic data allowed findings of an equivalence among ultrasound values and the stages of fibrosis (already established based on the histological data). It can be assumed that ARFI-Q sonoelastography could at least partially replace the biopsy examination of the liver, limiting the discomfort and potential complications related to the invasive procedure.

Another limitation is that the majority of people included in this study underwent periodic conservative treatment of lymphoedema (manual lymphatic drainage and elastic compression bandage), complemented by regular use of elastic compression garments. It has been pointed out that short stretch compression softens fibrotic tissues[29]. Our results could have been affected by the uses of such elastic garments as the compression of the upper layers could have influenced the elasticity of upper and lower part of subcutaneous tissues.

5. Conclusions

The present study demonstrates the usefulness of ARFI-Q elastosonography in identifying some transformations of lymphoedematous epifascial tissues. Although further research on various features of this measurement approach is needed, there is no doubt about its usage in the study of lymphoedema. It does not demonstrate greater invasiveness than other types of measurement, but maybe more expensive compared to the cheaper ultrasound exam.

There is a need of an increase of ARFI-Q investigations, in order to collect more sonoelastographic data related to lymphoedematous tissues. Comparing sonoelasto-graphic data with those of other methods of

lymphoedema assessment, which are capable of identifying the tissue changes, could lead to greater advances in lymphoedema management. Such an approach has been seen in liver pathologies, where a comparison between ARFI data and tissue microbiopsies performed at the same area has led to more precise monitoring of the extent of fibrosis as well as identifying the type of cells involved. MRI examination, performed with T2 images and fat suppression and Flair sequences, could allow a correlation of ARFI values with the entity of water, fibrosis and lipoid degeneration in lymphoedematous tissues. Such an approach could be initially reserved for cases at the upper and lower limits of the observed range, for a gross distinction of tissue pattern and morphology. Finally, it seems promising to carry out ARFI investigation on other pathological conditions, which determine a definite transformation of the subcutaneous tissue (as in the case of obesity, dermatoliposclerosis and/or systemic sclerosis), in order to observe whether homogeneous elastometric values can be obtained, as a reference.

Author Contributions

Conceptualization, AO and GB; methodology, AO, GB and SF; formal analysis, AO; writing-original draft preparation, AO, GB, SF and NG; writing-review and editing, AO, GB, SF and NG. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study

Conflicts of Interest

The authors declare no conflict of interest.

References

1) Tiwari A. Differential Diagnosis, Investigation and Current Treatment of Lower Limb Lymphedema. Archives of Surgery 2003, 138, 152, DOI: 10.1001/archsurg.138.2.152.

2) Golshan M, Smith B. Prevention and management of arm lymphedema in the patient with breast cancer. J Support Oncol 2006, 4, 381-386.

3) Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz T, Perkins GH, Elting LS. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol 2009, 27, 2007-2014, DOI: 10.1200/jco.2008.18.3517.

4) Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol 2008, 26, 5689-5696, DOI: 10.1200/jco.2008.16.4731.

5) Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, Boccardo F. Microsurgery for lymphedema: clinical research and long-term results. Microsurgery 2010, 30, 256-260, DOI: 10.1002/micr.20737.

6) Kim W, Chung SG, Kim TW, Seo KS. Measurement of soft tissue compliance with pressure using ultrasonography. Lymphology 2008, 41, 167-177.

7) Sener SF, Winchester DJ, Martz CH, Feldman JL, Cavanaugh JA, Winchester DP, et al. Lymphedema after sentinel lymphadenectomy for breast carcinoma. Cancer [Internet]. 2001;92(4):748–52. DOI: 10.1002/1097-0142(20010815)92:4<748::aid-cncr1378>3.0.co;2-v.

8) The diagnosis and treatment of peripheral lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology 2016, 49, 170-184.

9) Ruocco V, Brunetti G, Puca RV, Ruocco E. The immunocompromised district: a unifying concept for lymphoedematous, her-pes-infected and otherwise damaged sites. J Eur Acad Dermatol Venereol 2009, 23, 1364-1373, DOI: 10.1111/j.1468-3083.2009.03345.x.

10) Chen HC, O'Brien BM, Pribaz JJ, Roberts AH. The use of tonometry in the assessment of upper extremity lymphoedema. Br J Plast Surg 1988, 41, 399-402, DOI: 10.1016/0007-1226(88)90081-1.

11) Bagheri S, Ohlin K, Olsson G, Brorson H. Tissue tonometry before and after liposuction of arm lymphedema following breast cancer. Lymphat Res Biol 2005, 3, 66-80, DOI: 10.1089/lrb.2005.3.66.

12) Forte AJ, Huayllani MT, Boczar D, Cinotto GJ, McLaughlin SA. Ultrasound elastography use in lower extremity lymphedema: a systematic review of the literature. Cureus 11 (9): e5578.DOI

13) Lim CY, Seo HG, Kim K, Chung SG, Seo KS. Measurement of lymphedema using ultrasonography with the compression method. Lymphology 2011, 44, 72-81.

14) Wells PN, Liang HD. Medical ultrasound: imaging of soft tissue strain and elasticity. J R Soc Interface 2011, 8, 1521-1549, DOI: 10.1098/rsif.2011.0054.

15) Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, Correas JM, D'Onofrio M, Drakonaki EE, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med 2013, 34, 169-184, DOI: 10.1055/s-0033-1335205.

16) Palmeri ML, Wang MH, Dahl JJ, Frinkley KD, Nightingale KR. Quantifying hepatic shear modulus in vivo using acoustic radiation force. Ultrasound Med Biol 2008, 34, 546-558, DOI: 10.1016/j.ultrasmedbio.2007.10.009.

17) Karlas T, Pfrepper C, Wiegand J, Wittekind C, Neuschulz M, Mössner J, Berg T, Tröltzsch M, Keim V. Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease. Scand J Gastroenterol 2011, 46, 1458-1467, DOI: 10.3109/00365521.2011.610004.

18) Yoneda M, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K, Saito S, Nakajima A. Nonalcoholic fatty liver disease: US-based

acoustic radiation force impulse elastography. Radiology 2010, 256, 640-647, DOI: 10.1148/radiol.10091662.

19) Tomita H, Hoshino K, Fuchimoto Y, Ebinuma H, Ohkuma K, Tanami Y, Du W, Masugi Y, Shimojima N, Fujino A et al. Acoustic radiation force impulse imaging for assessing graft fibrosis after pediatric living donor liver transplantation: a pilot study. Liver Transpl 2013, 19, 1202-1213, DOI: 10.1002/lt.23708.

20) Bruno C, Caliari G, Zaffanello M, Brugnara M, Zuffante M, Cecchetto M, Minniti S, Pedot A, Talamini G, Pozzi-Mucelli R. Acoustic radiation force impulse (ARFI) in the evaluation of the renal parenchymal stiffness in paediatric patients with vesicoureteral reflux: preliminary results. Eur Radiol 2013, 23, 3477-3484, DOI: 10.1007/s00330-013-2959-y. 474.

21) Onorato A. La elastosonografia con tecnica ARFI (Acoustic Radiation Force Impulse) per lo studio delle modificazioni dei tessuti epifasciali nel linfedema dell'arto superiore [Acoustic Radiation Force Impulse (ARFI) elastosonography for the study of epifascial tissue modifications in upper limb lymphedema]. PhD dissertations directory of Udine University:; 2014. Available from: https://hdl.handle.net/11390/1132670

22) Mohamadnejad M, Tavangar SM, Sotoudeh M, Kosari F, Khosravi M, Geramizadeh B, Montazeri G, Estakhri A, Mirnasseri MM, Fazlollahi A et al. Histopathological Study of Chronic Hepatitis B: A Comparative Study of Ishak and METAVIR Scoring Systems. Int J Organ Transplant Med 2010, 1, 171-176.

23) DeJong HM, Abbott S, Zelesco M, Kennedy BF, Ziman MR, Wood FM. The validity and reliability of using ultrasound elastography to measure cutaneous stiffness, a systematic review.Int J Burn Trauma 2017; 7 (7): 124-141.

24) Sanderson J, Tuttle N, Laakso L. Acoustic Radiation Force Impulse Elastography assessment of lymphoedema tissue: an insight into tissue stiffness. Cancers 2022, 14, 5281.

25) Righetti R, Garra B, Mobbs L, Kraemer-Chant C, Ophir J, Krouskop T. The feasibility of using poroelastographic techniques for distinguishing between normal and lymphedematous tissues in vivo. Physics in medicine and biology 2007, 52, 6525-6541, DOI: 10.1088/0031-9155/52/21/013.

26) Chan WH, Huang YL, Lin C, Lin CY, Chen MH, Chu SY. Acoustic Radiation Force Impulse Elastography: Tissue Stiffness Measurement in Limb Lymphedema. Radiology 2018, 289, 759-765, DOI: 10.1148/radiol.2018172869.

27) Erdogan Iyigun Z, Agacayak F, Ilgun AS, Elbuken Celebi F, Ordu C, Alco G, Ozturk A, Duymaz T, Aktepe F, Ozmen V. The Role of Elastography in Diagnosis and Staging of Breast Cancer-Related Lymphedema. Lymphat Res Biol 2019, 17, 334-339, DOI: 10.1089/lrb.2018.0012.

28) Gasperoni C, Salgarello M. Rationale of subdermal superficial liposuction related to the anatomy of subcutaneous fat and the superficial fascial system. Aesthetic Plast Surg 1995, 19, 13-20, DOI: 10.1007/bf00209305.

29) Whitaker J, Williams A, Pope D, Elwell R, Thomas M, Charles H, Muldoon J. Clinical audit of a lymphoedema bandaging system: a foam roll and cohesive short stretch bandages. J Wound Care, 2015 Mar; 24(3):83-4; 86-90; 92-4.