

The Use of Noninvasive Imaging Techniques in the Assessment of Secondary Lymphedema Tissue Changes as Part of Staging Lymphedema

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Abstract

Too often, in clinical settings, the diagnosis and evolution of lymphedema is determined by limb circumference measurements and/or volume calculations. Besides the unrecognition of small lymphedemas, these techniques provide little to no information concerning the stage of the lymphedema. This latter is important in choosing appropriate treatment modalities and making an accurate prognosis. Different imaging techniques are described in literature giving insights in tissue changes due to lymphedema. The aim of this article is giving an overview of possible texture changes linked to the different edema stages, visualized with noninvasive imaging procedures like ultrasonography, computed tomography, dual-energy x-ray absorptiometry, or magnetic resonance imaging.

Introduction

IN WESTERN COUNTRIES, lymphedema mostly occurs as a complication after cancer therapy. Breast cancer-related lymphedema of the upper limb occurs frequently following breast cancer treatment and can be disabling. Breast cancer is the third most commonly diagnosed cancer worldwide (10.9% of all cancers). Furthermore, it is by far the most frequent cancer among women (23% of all new cancer cases in 2008).¹

The International Society of Lymphology (ISL) defines lymphedema as an “external manifestation of lymphatic system insufficiency and deranged lymph transport”.² In case of breast cancer-related lymphedema (BCRL), the disturbance of the lymph vascular system is caused by the operative dissection of axillary lymph nodes or irradiation. Lymphatic transport falls below normal capacity resulting in an interstitial accumulation of fluid, plasma proteins, extravascular blood cells, and parenchymal/stromal cell product, resulting in a chronic inflammation. Initially, lymph edema is soft and pitting, but in time, this stagnation of lymph fluid can change the skin and texture to be hard, brown, and fibrotic due to an excess deposition of extracellular matrix substances and adipose tissue, making lymphedema irreversible.³ It is clear that lymphedema evolves and gets worse in time when it is left untreated.⁴ Therefore, several institutions and authors have tried to define definitions for the several stages. One of these scales has been introduced by the ISL (Table 1).⁵

Although lymphedema is not life threatening, it may cause substantial complications, depending on the stage and whether the lymphedema is subjective or objective. In subjective lymphedema, patients should be aware of perceived swelling and sensations such as heaviness or tightness even before the onset of objective measurable edema. Besides clinical measurable swelling, symptoms of heaviness, weakness, pain, tension, and sensory deficit of the arm have been reported in literature on objective edema.^{6,7} Nevertheless, these subjective and/or objective symptoms can cause other complications as anxiety, maladjustment, social isolation, as well as physical discomfort, disability during activities of daily living, impaired function, and emotional stress.^{7–10}

When lymphedema is diagnosed in an early stage, conservative treatment (i.e., combined physical therapy (CPT)) could reduce the edema. Therefore, it is recommended to start as early as possible with physiotherapy after surgery and certainly once lymphedema is detected.¹¹ When CPT has clearly been unsuccessful, microsurgical procedures may be undertaken to alleviate/cure lymphedema by improving the lymph return to the blood circulation. It can even be used in addition to CPT to maintain the reduction of the lymph edema.⁵ There is an absolute need for reliable noninvasive diagnostic imaging techniques because there is no consensus on their use and only very few scientific publications on objective measurement techniques are available, nevertheless it is important to assess tissue alterations in its early stage.

TABLE 1. FOUR-STAGE SCALE FOR THE CLASSIFICATION OF A LYMPH-EDEMATOUS LIMB AS DESCRIBED IN THE INTERNATIONAL SOCIETY OF LYMPHOLOGY CONSENSUS DOCUMENT

Stage	Clinical manifestation
0 (Ia)	Latent/subclinical condition; swelling is not evident despite impaired lymph transport. It may exist months or years before overt edema occurs.
I	Early accumulation of fluid with relatively high protein content, disappears limb elevation (reversible lymphedema). Pitting may occur.
II	Spontaneous irreversible lymphedema: limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in stage II, the limb may/may not pit as excess fat and fibrosis supervenes.
III	Lymphostatic elephantiasis: trophic skin changes and pitting can be absent.

Clinically, the diagnosis of lymphedema is based mainly on patient history and self-report of symptoms, visual inspection and skin palpation, and the determination of volume differences between both limbs. Sequential circumference measurements along designated measure points are widely used. Consequently, limb volume can be calculated or estimated based on a truncated cone formula. Volumetry by means of water displacement is considered the golden standard. The study of Taylor et al. concluded that circumference measurements and the estimated volume were reliable, but overestimated volume by 110 mL, and the water displacement method has a measurement error of 150 mL.¹² In this way, early detection of stage 0 edema, dependent on volume measurements, is difficult and even patients with a mild stage I lymphedema (<150 mL) are being overlooked by the current measurements. Another consideration to be made is that these volume measurements are not only influenced by fluid changes but also by compositional changes of muscle mass, bone, or fat. For example, muscle hypertrophy or atrophy due to increased use or disuse, hand dominance, ... can obscure true limb differences.³ Perometry is an optoelectronic volumetry device, using a sliding frame with infrared beams and the resulting shadow, to calculate limb volume. In addition to the previously discussed disadvantages of the use of volume measurements, assessment with this device is also restricted to the arms and legs, without hands and feet, and due to the high cost, it is not frequently used.³ None of the previously described techniques assess possible tissue changes related to the stage of lymphedema.

Recently, bioelectrical impedance has been used to estimate the extracellular fluid content in limbs. Alternating current passes through skin surface electrodes and the impedance to the flow of the current is measured. This device should make it possible to detect early stage lymphedema, but it is not sensitive to fibrotic changes.³

The aim of this review is to give an overview of different noninvasive imaging procedures that visualize possible tissue alterations depending on the edema stage in patients with lymphedema.

Ultrasonography

Cutaneous ultrasonography is an easily feasible noninvasive technique, which is not limited in use in case of extremely

overweight or less mobile patients. Besides the low cost, it does not use ionizing radiation. Nevertheless, the main disadvantages of ultrasonography are the poor spatial resolution, the operator dependency, and the subjective evaluation of images. Different studies use high-frequency ultrasonography to describe changes in thickness and echogenicity of the dermis and subcutis in case of lymphedema.

Although all studies measure an increase in dermal and subcutaneous layer thickness, there is no consensus as to the degree of this increase.^{13–19} Patient characteristics, time since onset of lymphedema, device settings, and frequency of the ultrasound probe are factors influencing the image resolution and thereby the accuracy of thickness measurements.

In contrast to the findings concerning tissue thickness, different observations were made concerning tissue echogenicity and the subsequent texture changes.

An early study of 1992 with ultrasonographic imaging of edematous arms mentioned several changes of echodensity: a mild hyperechogenic dermis and a hypoechoic subcutis with reflective streaks.¹⁴ This increased streaking was consistent with diffuse fibrosis and chronic disease. Neither the underlying pathology (primary vs. secondary lymphedema) nor the stage of the lymphedema was taken into account. In contrast, Gniadecka²⁰ found a significant decrease of dermal echogenicity measured in 10 edematous legs (20 MHz transducer and gain settings at 22 dB). The excess of dermal fluid was found to be uniformly distributed in the upper and the lower dermis.²⁰ The latter was confirmed in a study of Van der Veen et al.¹⁶ with 22 patients with clinical lymphedema (interlimb circumference difference >2.5 cm) present for a mean time period of 5 years. Echogenicity of the edematous dermis was found to be significantly decreased, and the subcutaneous echogenicity was increased, although these results were not statistically significant.¹⁶ A possible explanation for the latter results can be the fact that they included patients only based on a circumference difference more than 2.5 cm, without any correction of arm dominance or the side of surgery. This definition of clinical lymphedema does not take the edema stage into account, making no distinction between images from patients with acute, stage I, or chronic, stage II–III, lymphedema. Grouping all individuals with lymphedema together, regardless of the stage, may obscure significant echogenicity outcomes. Based on a questionnaire, retrospectively, they mentioned that the lymphedema was present for 5 years, but no further information was recorded giving an idea of the stage.

Subsequent studies have shown that not only the average gray scale value is of importance in analyzing tissue composition but also that an edematous subcutis is represented by different patterns, depending on the edema stage and underlying texture changes.

Balzarini et al.¹⁵ reported an increase in subcutaneous thickness in 46 patients with chronic stage III lymphedema and described three ultrasound patterns: primary fluid accumulation with large lymphatic lacunae, fibrosclerosis, and a mixed picture. Ultrasonographic images of patients with a clinical impression of having “soft” lymphedema showed mainly fluid accumulation (68.4%), pitting was present in 89.4% of them. In 76.9% of the patients diagnosed with “hard” edema, ultrasound showed diffuse fibrosis, and in 14.2%, a mixed pattern was visualized, none of them had pitting edema. In patients having “mild” edema, the three patterns were found, none of them having pitting edema.¹⁵ In this study, ultrasound patterns were

not associated with interlimb volume differences, or with time since onset of the lymphedema. The study of Fumiere et al., where ultrasound images were made of four biopsies, visualizes edematous subcutis being diffuse hyperechogenic as well as being hypoechoic with areas of hyperechogenicity.²¹ Although no detailed clinical data were mentioned in this article, this study confirms the existence of different subcutaneous ultrasound patterns. Dimikakos et al. showed, especially in case of chronic (primary and secondary) lower limb lymphedema, a homogeneous echogenicity, with an irregular pattern of hyperechogenic areas demarcated by thin hypoechoic bands resulting in a stone-paved picture, and the absence of the echogenic band mesially to the subcutaneous tissue.²²

Tassenoy et al.¹⁸ defined different patterns of subcutaneous changes comparing ultrasound with magnetic resonance imaging (MRI). All seven patients showed a homogeneous hypoechoic dermal appearance compared to the healthy side, due to excess interstitial fluid scattered among the collagen tissue of the skin. The subcutis showed different patterns of texture changes, mainly depending on the duration of lymphedema. In patients with a rather recent onset, a more or less uniform hypoechoic appearance of the subcutis was visualized, caused by the presence of fluid, diffusely spread within the adipose tissue. This pattern was less present in patients with chronic edema. A second pattern was hyperechogenic areas surrounded by hypoechoic streaks, explained as adipose tissue surrounded by fluid organized in trabecular structures. Patients with an established chronic edema showed a homogenous hyperechogenic appearance, due to overall overgrowth of adipose tissue.¹⁸ These latter two patterns were also described in other studies.^{16,21} This study showed no consistency between increasing arm volume differences measured by water displacement and the progression in edema stage. Patients with mainly acute, fluid-like images had volume differences between 8% and 32%, whereas the volume difference in patients with ultrasound images suggesting a chronic stage was spread between 9% and 61%.

Lim et al.¹⁷ added a calculation of “resistance of compression” (RC), by measuring tissue thickness after maximal compression, indicating the tendency to deform as a result of compression. RC was defined as the difference between the initial thickness without compression and the thickness with maximal compression over the initial thickness. The RC in the edematous skin and subcutis was significantly smaller than in the control arm, indicating that edematous tissues become stiffer. Only body mass index (BMI) was found to be correlated with the subcutaneous RC. The subcutis of obese edema patients is likely to be less stiff and more elastic than of slender patients. Neither the duration of edema nor other demographic or clinical data were found to be correlated with RC.¹⁷ They did not make the distinction between acute versus chronic edema, calculating the RC value. Possibly, patients with stage I pitting lymphedema show larger RC, pushing fluid aside in case of maximal compression with the ultrasound transducer, than patients with stage III nonpitting lymphedema. The therapeutic effects of a 2-week CPT program in 20 patients with breast cancer-related lymphedema was evaluated by Lee et al. measuring soft tissue thickness and the latter RC by ultrasonography.²³ After treatment, the soft tissue thickness was significantly reduced at the elbow and upper arm, but not at the lower arm. A trend to increased compliance was measured at each of the three points, although not significant. The remark

can be made that 75% of the subjects had lymphedema of stage II or higher, with fibrosis being more prominently present and making these subjects less responsive to treatment. Probably, the results in case of subjects with stage I would be more pronounced. Tissue echogenicity was not taken into account.

Computed Tomography

Although computed tomography (CT) scanning can provide images with an excellent spatial and temporal resolution, the major disadvantage is the exposure to highly ionizing radiation.

Studies investigating lower limb lymphedema described CT findings as follows: (1) skin and (2) subcutaneous thickening,^{24–26} (3) honeycomb pattern suggested being fat pockets surrounded by septa-like structures composed of fluid, fibrous tissue, or both,^{24–26} (4) fat lobules being taller than wide,²⁴ (5) muscular enlargement in 21% of the patients due to hypertrophy on the increased weight of lymphedematous limbs,^{24,26} although Hadjis et al. detected no changes in the subfascial compartment, and (6) in 26%, the interstitium was thickened with multiple layers of water and fat with distinguishable septa.²⁴

Brorson et al.²⁷ assessed 11 women with chronic upper limb lymphedema of the non-pitting using volume rendered-CT (VR-CT) images to confirm the presence of excess adipose tissue and compared this technique with the results from water displacement and the aspirated volume after liposuction. VR-CT allows analysis of the volume of different parts (adipose tissue) of the arm. Between the water displacement technique and volume estimation using VR-CT, a strong correlation (correlation coefficient (CC) = 0.996) was found for preoperative arm volume and excess volume (CC = 0.986). After surgery, the mean aspirated volume showed strong correlations with excess volumes estimated with VR-CT and water displacement, respectively, CC = 0.973 and CC = 0.985. VR-CT is not only used to make an estimation of the excess of volume in the edematous limb but is also used to make an estimation of the excess of adipose tissue in those limbs. The mean volume of adipose tissue that was removed during surgery was 1356 mL. VR-CT estimated this mean excess of adipose tissue on 1251 mL (81% of volume excess), which provides a strong correlation (CC = 0.977). According to this study, VR-CT can not only be used to make an estimation of the excess of volume in the edematous arm but also can be more precise and estimate the excess of adipose tissue in patients with nonpitting (chronic) edema.²⁷

Dual-Energy X-Ray Absorptiometry

Dual-energy x-ray absorptiometry (DXA) is a two-dimensional scanning technology, providing quantitative measurements of lean (fat free mass), bone (bone mineral content), or fat (fat mass) volumes. Advantages of DXA are easy to perform, computer-based registration, data analysis of selected regions, and the use immediately after surgery or with patients with skin disorders. Disadvantages are the exposure to ionization radiation, difficulties with non-cooperating patients, and repeatability for follow-up comparisons. In the study of Gjorup et al.,²⁸ volume measurements with DXA were compared with water displacement method and circumference measurements and the inter- and intraobserver reliability of the three methods were assessed. DXA showed the narrowest limits of agreement of the differences between two subsequent measurements of each

observer, had lower absolute and relative technical errors of the measurements, and had higher inter and intrarater correlation coefficients. The best agreement of volume estimation was found between the DXA method and the water displacement. The latter technique significantly underestimated small lymphedemas and overestimated large edemas. Between DXA and circumference measurement, there was no systematic bias.²⁸ Santin and Ward reported high correlations ($p < 0.0001$) between the DXA-calculated volumes and the optoelectronic volumetry, measuring upper limbs of healthy subjects.²⁹ Similar high correlations ($r = 0.996$, $p < 0.0001$) were found in a study comparing DXA-calculated volumes and arm volumes derived from water displacement of 18 patients with nonpitting edema.³⁰ Based on DXA analysis, measurements showed that the fat mass increased with 73 (43–111)%, the fat-free mass with 47 (13–81)%, and the mineral bone content with 7 (–12 to 32)%, concluding that adipose tissue as well as increased muscle mass contributed to the excess volume of lymphedematous tissue. The latter was hypothesized as muscle hypertrophy due to years of higher mechanical load.³⁰ Cherniec et al.³¹ examined tissue changes in nine patients diagnosed with early grade II pitting edema and, in particular, whether these changes were localized to certain regions of the arm. While the volume of affected arm was significantly higher than the unaffected arm, this significant difference was also found in each arm segment, with the distal arm being the most affected. Extracellular fluid assessment by bioimpedance spectroscopy (BIS) also revealed the greatest differences within this part of the arm. The absolute fat and lean tissue mass were significantly higher in the affected arms compared to the unaffected arms, and taken arm dominance and edema side into account, patients in whom the nondominant arm was affected had a greater difference in fat mass, but a smaller difference in lean mass between both arms compared to women in whom the dominant arm was affected. The largest differences in fat mass and fat-free mass were found in the regions around the elbow.³¹ In a study of Newman et al.³², the precision of DXA was determined in 24 patients with grade II unilateral lymphedema. Circumferential measurements showed a volume difference of 13.8% between both arms. Except for bone mineral content, all other variables (DXA fat, lean mass and total arm volume, and BIS extracellular fluid and total fluid volume) were significantly ($p < 0.0001$) increased in the edematous arm. Based on these results, a change in ≥ 57.3 g of fat measured with DXA would indicate a significant change with a 95% confidence level of the fat mass, or an increase of 43.7 mL extracellular fluid measured with BIS would indicate a significant change at a 95% confidence level. In this study, the significant increase in the lean mass of the edematous arm is explained as the fact that lean mass measurements not only include muscle volumes but also all the other tissue components (proteins, glycogen, water, ...) except for fat and bone minerals, with a possible contribution of growth of fibrotic tissue in chronic lymphedema patients.³² Dylke et al.³³ used DXA to measure the different tissue volumes (fat, lean, bone, and total) in edematous arms and compared these results with the clinical outcomes based on perometry and BIS and with a healthy control group, matched for age and BMI. Based on their study results, they concluded that volumes of fat and lean tissue are related to severity of lymphedema and to which side is affected.³³ BMI and duration and severity of lymphedema were factors identified as being significantly related to the in-

terlimb fat difference, but only in the subgroup with non-dominant side lymphedema. Increased adiposity was found in edematous arms, but in case of nondominant side lymphedema, the unaffected dominant side also had more fat compared to healthy controls. They conclude that these results suggest that the increase in fat volume is not only related to the lymphedema but, combined with the decrease in muscle volume, also due to a lack of physical activity, in turn, increasing the risk of developing lymphedema.³³ This decrease in muscle volume is in contradiction with the previous described studies.^{30,32} The significant correlation between the total excess arm volume (difference in arm volume between the swollen and the non-swollen arm) and the excess of muscle volume ($r = 0.970$, $p < 0.0001$) on one hand and the excess arm volume and excess fat volume on the other hand ($r = 0.979$, $p < 0.0001$) was also found in the study of Brorson et al. Although in contradiction to the study of Dylke et al., the duration did not correlate with volume measurements.³⁰ In this study, arm dominance and edema side were not taken into account and the mean duration of lymphedema (11 years) was also much longer than in the study of Dylke et al.³³ (41 months), assuming a more advanced edema stage in the first study.

Magnetic Resonance Imaging

MRI is a safe, noninvasive technique that provides excellent contrast for visualizing soft tissues without the exposure to ionizing radiation. Depending on the sequence setting, the signal intensity of water and fat will change.

Several studies^{22,34–37} reported (asymmetrical) dermal thickening and a hyperintense T2-weighted signal, indicating a high water content interspersed within the dermal interstitium, even in patients with low-grade lymphedema.³⁸ Case et al.³⁵ also visualized small and large serpiginous “channels” or “lakes” suggesting dilated dermal lymphatic collaterals.

Early MRI studies^{22,34–36,39–41} of patients with chronic (lower) limb lymphedema have recognized the presence of subcutaneous changes. Besides thickening, dilated dermal lymphatics or “lakes” with sequestered fluid, displaying a honeycomb pattern, are described, suggesting the accumulation of fluid between fat surrounded by fibrotic tissue,^{36,39–42} a widening of interlobular partitions³⁷ dilated collateral lymph vessels.³⁴ According to the study of Haaverstad et al.,⁴¹ this honeycomb pattern was not present in lymphedema of less than 1 year of duration and in the study of Sagen et al.,⁴³ validating a simplified water displacement instrument, all women diagnosed with arm lymphedema based on a 10% volume difference with the healthy control arm showed an increased signal intensity in the subcutaneous tissues on the T2-weighted sequences arranged in this honeycomb pattern. The presence of an increased signal intensity without clinically defined lymphedema was found in two patients, explained as subclinical stage 0, by the authors.⁴³

In the study of Case et al., the hypointense signal on T1-weighted images and the homogenous hyperintense signal on T2-weighted sequences, are explained as extensive subcutaneous edema and increased subcutaneous fat.^{35,36} Haaverstad et al.^{41,42} observed besides the honeycomb pattern, a diffuse reticular pattern with hyperintense signals on T2-weighted images, explained as large fluid collections within dilated lymphatic vessels or pathways. In the study of Idy-Peretti et al.,³⁷ fattening of the connective tissue is described, with an

enlargement of fat lobules of 80% in the superficial layer and only 60% in the deep subcutaneous layer.

Different MR image sequences and MR spectroscopy made of four lymphedematous tissue biopsies were compared with ultrasound (US) findings.²¹ Hyperechogenic areas on US corresponded with either a hyposignal in all sequences or a low water peak on spectroscopy suggesting the presence of fibrosis, or with a hyposignal in T1, hypersignal in T2 fat-suppressed images, or a high spectroscopic water peak indicating fluid accumulation. This study confirms that intralobular changes in chronic lymphedema are due to fibrosis.²¹

Gardner et al.³⁸ observed three patterns of edematous subcutaneous tissue with 3.0 T MRI, providing a better signal and a superior contrast between water and fat. T1-weighted Water Selective Cartilage Specific sequence is an acquisition protocol giving a hypersignal for proteinaceous edema; while suppressing the fat signal, T2-weighted Short Tau Inversion Recovery (STIR) gives a hyposignal for fat and a hypersignal for edema or fluid, specifically used to determine edema within the muscle. A first pattern was the result of an abnormally increased signal on T2 STIR sequence in patient with a rather recent onset of lymphedema. This pattern was also found in the study of Tassenoy et al., hyperintense signals spread through the subcutis on T2 turbo spin echo-weighted images with fat suppression, indicating the spread of fluid.¹⁸ A second honeycomb pattern with a high signal trabecular pattern representing fluid interspersed between low signal fat modules and commonly associated hyperintense signals along the muscle fascia representing epifascial fluid.^{18,38} The third pattern commonly observed in patients with chronic edema, is the result of a uniform hypointense T2-weighted STIR image due to fat hypertrophy.^{18,38}

Studies of Lu et al.⁴⁴ and Li et al.⁴⁵ measured soft tissue thickness by means of fat-suppressed T2-weighted mid-axial plane images of the lower limb in patients with different stages of secondary lymphedema and compared results with volume measurements by water displacement. Between the different stages, significant differences in total soft tissue thickness, thickness of the subcutaneous layer, volume of the affected calf, and differences between affected and unaffected calf of these three measurements were found. Between stage 0 and 1, no significant differences were demonstrated in volume measurements by the water displacement method. This study concluded that for staging lower limb lymphedema, the difference in subcutis thickness between the affected and unaffected calf (DSTT) showed the best discrimination ability among all parameters.^{44,45} DSTT cutoff values for classifying stage 0 versus 1, stage 1 versus 2, and stage 2 versus 3 were set at respectively 3.5, 11.5, and 29.3 mm.

The signal depicted from the subfascial tissues was normal in most studies, without remarkable changes in the muscle compartment.^{22,34,35,40-42}

Conclusion

Although circumference or volumetric measurements are standardly used to diagnose or evaluate progression of lymphedema in clinical settings, these assessment techniques provide little to no information regarding the stage of the lymphedema. Yet, this is important in choosing the appropriate treatment. On the other hand, imaging techniques, each

with their own advantages and disadvantages, can provide insights into this matter.

In literature, little studies are found concerning the diagnosis of *subclinical lymphedema*. Besides the diagnosis based on patient's self-reported signs and symptoms, one study mentioned the presence of an increased signal intensity on dermal T2-weighted MRI sequences in patients without clinically defined lymphedema, indicating the presence of dermal water.⁴³

All techniques visualize possible increased thickness of the dermal and subcutaneous layer in case of *clinical lymphedema*.

On ultrasonographic images, hypoechogenicity of the subcutis compared to the normal healthy side is rather linked with an *acute stage I pitting lymphedema*, due to extracellular fluid dispersed within the interstitial matrix. Furthermore, hypoechogenic areas at the fascia are described as epifascial fluid lakes.^{15,18} On MRI images, these patients show hyperintense signals on T2-weighted sequences with fat suppression within the dermis, spread throughout the subcutis and epifascial fluid collections.^{18,43}

DXA measures increased fat and lean tissue mass in *early grade II pitting lymphedema*.^{31,32} Interlimb fat difference is greater in patients of whom the nondominant arm is affected, probably due to a lack of physical activity.³² Increase of fat mass in the unaffected dominant arm strengthens this assumption.³³

The *chronic stage of lymphedema* is recognized on ultrasound by hyperechogenicity of the subcutis, together with hyperechogenic streaking due to fibrosis formation. Hyperechogenicity is often linked with adipose tissue formation. In one study, 76% of the patients with "hard" edema, fibrosclerosis dominated the picture and in 14%, a mixed pattern of lymphatic lacunae and fibrosclerosis was found. "Resistance to compression" could provide some additional information concerning the stiffness of tissues, although the influence of the edema stage should be further examined. MRI and CT provide superior image quality. In a more advanced stage of edema, hyperintense honeycomb patterns on T2-weighted images (with fat suppression) indicate the presence of fat pockets surrounded by fluid-filled fibrotic trabecula, fluid collections within dilated lymph vessels.⁴² Additional spectroscopic high water peaks indicate the fluid accumulation.²¹ Hypointense T2-weighted images with fat suppression and homogenous hypointense T1- and hyperintense T2-weighted images indicate fat hypertrophy.^{38,35} Hypointense images on all sequences combined with low spectroscopic water peaks are suggestive for fibrosis.²¹ One study quantitatively assessed lower limb lymph edema by linking subcutaneous thickness of the calf to the stage of edema.⁴⁴ Further studies should define these cutoff points for the different stages of upper limb lymphedema. Honeycomb patterning and enlargement of fat lobules are also visualized on CT.²⁴⁻²⁶

Related to the severity of the lymphedema and to which side is affected,³³ DXA volume measurements show significantly increased fat and fat-free mass in stage III lymphedema.³⁰ The volume of the fat-free mass is not only determined by the muscles but also by fluid and fibrotic tissue. Depending on the edema stage, both components can influence results, making it difficult to make a statement on the edema stage based on the fat-free mass. Natural interlimb volume differences, muscle atrophy due to physical inactivity, or muscle hypertrophy due to the extra load of the edematous arm, are other points of

discussion in literature. These aspects could give a distorted picture to define the severity of lymphedema and the true nature of the tissue changes when circumference or volume measurements would be used to diagnose lymphedema. These issues can be clarified by proper interpretation of different imaging procedures.

All the above shows that, based solely on left–right limb volume difference, it is a too short-sighted approach to make statements about the severity of lymphedema, the possible treatment strategies, and their prognosis.

Author Disclosure Statement

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