LYMPHATIC RESEARCH AND BIOLOGY
Volume 21, Number 5, 2023

DOI: 10.1089/lrb.2022.0101

Tissue Dielectric Constant and Skin Stiffness Relationships in Lower Extremity Lymphedema

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Abstract

Background: Lower extremity lymphedema or edema (LELE) may progressively transition from a state of excess tissue fluid to increased fat accumulation and collagen deposition, with tissue fibrosis and hardening. Such changes may lead to altered tissue water holding and thereby impact tissue dielectric constant (TDC). This study seeks to evaluate the relationship between TDC and tissue indentation force (TIF) in patients with LELE and assess the utility of the leg/arm TDC ratio (LAR) as an indicator of LELE.
Methods and Results: Thirty females (49–91 years) with previously diagnosed LELE were evaluated during a scheduled session. TDC and TIF were measured 8 cm proximal to the medial malleolus on the medial and lateral aspects of both legs and on one forearm 8 cm distal to the antecubital fossa. The TDC–TIC relationship and the LAR were subsequently determined. Main results showed an absence of a significant correlation between TDC and TIF on medial or lateral leg sites but a positive correlation on the normal forearm site. Further, LAR values exceeded the published proposed threshold of 1.35 for 29/30 patients when using medial-side TDC values and 28/30 patients when using lateral-side TDC values.
Conclusions: Findings suggest that for patients with LELE, TDC values are significantly elevated on medial and lateral standardized sites. The LAR determined using either medial or lateral sites that are similar to each other and have values consistent with a lymphedema threshold of 1.35. In edematous legs of the type evaluated herein, there is no apparent relationship between TDC values and indentation force.

Keywords: lymphedema, collagen, tissue fibrosis, dielectric constant, lower extremity edema, indentation, hardness

Introduction

The potential effects of chronic lymphedema on collagen accumulation were brought to the research community's attention a number of years ago.[1] Studies on mice have shown that lymph stasis is associated with increased fat deposition, collagen deposition, and fibrosis.[2] In this animal model, the role of inflammatory cells has been well described,[3,4] and more general aspects of tissue changes have been reviewed.[5] Thus, the manifestations of chronic edema or lymphedema may progressively transition from a state of excess tissue fluid to increased fat accumulation and collagen deposition, with associated tissue fibrosis causing hardening of the involved tissue. Such changes may lead to reductions in relative water holding content and tissue dielectric constant (TDC).[6–8] An unanswered question is the extent to which these tissue changes impact measurement methods designed to detect or track lymphedematous changes over time or with treatment.

Methods such as bioimpedance spectroscopy,[9–11] or TDC that use measures of tissue water as indicators of arm[12–18] or leg,[19–23] lymphedema may be particularly susceptible. In fact, some work has reported a positive correlation between lower extremity skin stiffness and lymphedema stage and

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tissue water percentage.[24,25] Thus, one of the main aims of the present study was to evaluate possible relationships between lower extremity TDC values and tissue stiffness assessed via tissue indentation force (TIF) in patients diagnosed with lower extremity lymphedema or edema (LELE). Because such relationships and their comparisons among groups depend on variability features of both skin stiffness and TDC measurements, variabilities of sequential individual measurements in terms of their coefficient of variation were also of interest.[26]

A second aim was to evaluate the utility of a threshold value for the detection of lower extremity lymphedema, calculated from the ratio of leg to forearm TDC values, based on measurements in nonedematous legs.[21] Because site-dependent variations in TDC values are known to be present in patients with upper extremity lymphedema,[15] the question of whether TDC measurements made on medial versus lateral leg sites significantly differ in patients with lower extremity edema was also of interest.

Methods

Subjects

Inclusion criterion for participation in this study was that the subject be female, with previously diagnosed LELE, who was scheduled for a treatment session at a participating local lymphedema treatment clinic. Thirty females participated and each was advised of the nature of the study before starting measurements, and each signed an approved University Institutional Review Board informed consent (No. 2019-515). Patients were included sequentially as available, subject to the following exclusionary criteria: (1) any open wound near an intended measurement site or (2) any implanted wires or electronic medical devices. The 30 patients evaluated ranged in age from 49 to 91 years, with body mass index ranging from 14.9 to 65.9 Kg/m^2. The duration of their lower extremity condition ranged from 1 to 40 years.

Table 1 summarizes the main presenting features and the target leg and arm sides measured. Of the 18 patients with lower extremity edema, all had diagnoses of chronic venous insufficiency, and of the 12 patients with lower extremity lymphedema, all had diagnoses of secondary lymphedema.

Measurements

TDC measurements were done with a compact hand-held device (MoistureMeterD Compact, Delfin Technologies, Kuopio, Finland), the operating principles and use of which have been previously described.[27] In brief, measured TDC values are largely dependent on water within the measured local volume and is a dimensionless number equal to the ratio of tissue permittivity to vacuum permittivity. The effective measurement depth of the device used is between 2.0 and 2.5 mm, so that epidermis and dermis are in their measurement volume. The TDC measuring device operates as an open-ended transmission line.[6,28] In use, a low-level 300 MHz signal is activated and transmitted into the skin when the sensor part of the device is in contact with the skin. Certain features of the reflected signal allow for the calculation of the complex reflection coefficient from which TDC values are determined.[7,29,30]

After about 5 seconds of skin contact, the percentage of tissue water that is calculated from the measured TDC value, is displayed on a digital screen on the device. In the present study, TDC measurements were made in triplicate at each of three standardized sites (two leg sites and one arm site), with measured values reported as the average of the triplicate values. The standard leg sites used were located 8 cm proximal to the middle of the medial malleolus with one measurement site on the medial aspect (shown in Fig. 1) and the other on the lateral aspect approximately opposite (180°) to the medial site (not shown). The middle of the medial malleolus as a reference point was chosen to be consistent with prior TDC measurement data.

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Measurements were done with the patient supine but not started until they had been supine for at least 10 minutes. The temporal measurement order was forearm, medial leg, and lateral leg. Following completion of all TDC measurements, TIF was determined at the same anatomical sites and in the same measurement order using the SkinFibrometer (Delfin Technologies) that is based on refinements to a skin

Table 1. Patient Features

	Lower extremity edema	*Lower extremity lymphedema*	p	*Combined*
Diagnosis, *N* (%)	18 (60)	12 (40)		30
Age (years)	77.8 ± 11.4	76.6 ± 11.2	0.755	77.3 ± 11.2
BMI (Kg/m^2)	32.1 ± 10.0	32.6 ± 11.3	0.884	32.3 ± 10.4
Duration (years)	6.6 ± 6.2	14.7 ± 12.4	0.079	9.8 ± 9.9
Target leg measured = Right, *n* (%)	7 (38.9)	8 (66.7)		
Arm measured = Dominant, *n* (%)	7 (38.9)	7 (58.3)		

Table values are mean ± SD. Duration is the number of years the lower extremity condition has been present. The *p*-values are based on Mann–Whitney tests. The target leg was the leg that had the greater visually observed swelling and the forearm measurement was on the same side as the target leg. Right indicates the right leg was the target otherwise it was the left. Dominant indicates if the arm measurement was on the dominant side, otherwise it was on the nondominant side.

BMI, body mass index; SD, standard deviation.

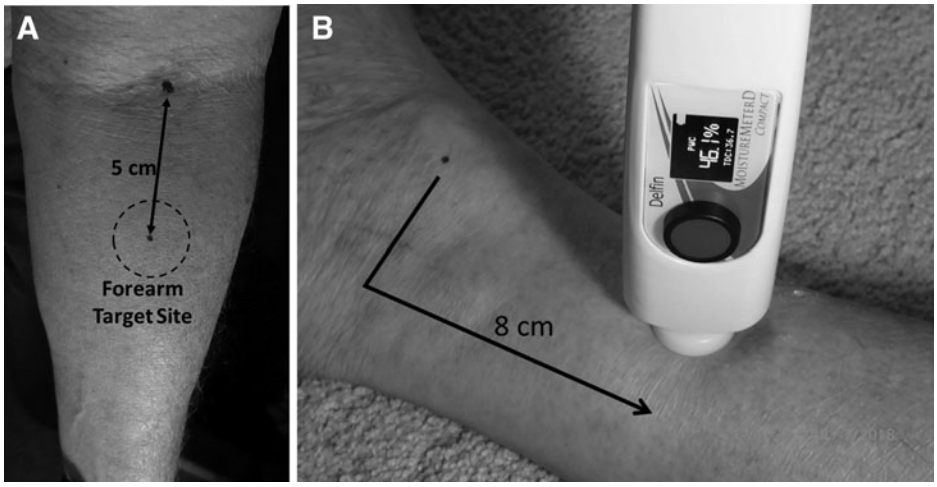

FIG. 1. Measurement sites. The forearm measuring site is shown in **(A)** and the medial leg measurement site is shown in **(B)**. The lateral leg measuring site (not shown) is circumferentially located 180° from the medial site. The TDC measuring device is shown in **(B)** as it would be applied. TDC, tissue dielectric constant.

indentation approach.[31–34] The SkinFibrometer measures skin stiffness or firmness based on the indentation force in milliNewtons (mN) required to indent skin 1.3 mm. With this hand-held device, the skin is lightly touched, whereupon a 2 mm diameter indentor is caused to deform skin inwardly with the resultant force recorded and displayed.[24,25,35,36] The device is equipped with internal sensors that accept measurements only within prescribed limits of force and force application velocity.

Thus, if an applied pressure is too large or applied too slowly or rapidly, internal software prompts to repeat the measurement. The standard device internally averages five consecutive measurement values and displays the average. In this study, each of the five consecutive repeated values was individually recorded so that the measurement coefficient of variation could be determined. The average of the five was used to represent the TIF value at each site. All measurements were done while participants were supine for at least 10 minutes on a padded examination table with arms resting at their sides and shoes and socks removed. Leg circumferences were measured with a Gulick II tape measure at the location where the TDC measurements were made on both legs.

Analyses

Coefficient of variation of individual measurements (CVI) was calculated for each site based on the three repeated TDC measurements and the five repeated TIF measurements. Overall TDC and TIF variability was then determined as the overall mean and standard deviation (SD) of the CVI for the entire group of 30 patients. Tests for relationships between TDC and TIF were based on regression analysis done separately for each measured site. Tests for differences in TDC between medial and lateral leg sites were based on paired *t*-tests with statistical significance based on a $p < 0.05$. Leg/arm TDC ratio (LAR) were calculated as the leg value/forearm value for each patient using TDC values measured on the target leg lateral and medial aspects. These ratios were compared to the lymphedema threshold LAR of 1.35 previously reported.[21]

To determine the number of subjects to be included in the present study, TDC values and their standard deviations previously measured at the medial and lateral gaiter area in 22 nonedematous legs were used to calculate an overall mean and SD that was 36.7 ± 5.05.[21] The effect size (ES) was based on being able to detect a 10% difference (3.67) at an α-level of 0.05 with a power (1-β) of 95%. The number of subjects needed for the calculated ES (0.7267) was determined to be $N = 27$ using the software GPower, version 3.1.97.[37] It was decided to increase this by 10% yielding an N of 30.

Results

TDC and TIF values and variability

Table 2 summarizes leg TDC values measured at medial and lateral leg sites and TIF values measured at the leg lateral site along with the CVI. At the standard leg site (8 cm proximal to the middle of the medial malleolus) TDC values did not differ between medial and lateral measurements. Average values ranged narrowly from 48.3 ± 8.3 at the standard medial site to 47.5 ± 7.7 at the lateral site. TDC values on the contralateral leg differed slightly between medial and lateral sites presumably due to the slightly lower value measured at the medial location. However, corresponding values between the target and contralateral leg did not significantly differ, suggesting that most of the patients may have had bilateral conditions.

The CVI tended to be greater at lateral versus medial sites but was statistically greater ($p < 0.05$) only on the target leg. Forearm TDC values (28.0 ± 4.0) were significantly less than all measured leg values ($p < 0.001$). TIF values, measured at the standard lateral site, were quite similar on both legs and on average differed by <15 mN with CVI values both <20% on average. Forearm TIF values were significantly less than at any leg site ($p < 0.001$) and had a slightly lower CVI.

TIF–TDC relationship

Paired leg TIF–TDC values are plotted in (Fig. 2) along with the associated regression lines for TDC values

TABLE 2. TISSUE DIELECTRIC CONSTANT AND TISSUE INDENTATION FORCE VALUES AND INDIVIDUAL MEASUREMENT COEFFICIENTS OF VARIATION

	Standard site of target leg			*Standard site of contralateral leg*			*Forearm*	*Leg/Forearm TDC Ratios*	
Circumference (cm)	27.9 ± 6.6**			24.9 ± 5.2			24.8 ± 4.0		
	Medial	*Lateral*	*Average*	*Medial*	*Lateral*	*Average*	*Anterior*	*Medial*	*Lateral*
TDC values	48.3 ± 8.3	47.5 ± 7.7	47.9 ± 7.1	41.8 ± 11.1	46.8 ± 8.9*	44.3 ± 9.2	28.0 ± 4.0	1.787 ± 0.363	1.751 ± 0.287
TIF values (mN)		216.9 ± 149.8			229.6 ± 167.9		48.4 ± 19.9		
TDC_CVI (%)	3.38 ± 2.3	5.15 ± 4.94*		4.11 ± 7.4	4.78 ± 4.08		2.7 ± 2.6		
TIF_CVI (%)		17.6 ± 10.4			16.4 ± 11.9		14.0 ± 8.6		

Table entries are mean ± SD. TDC is the tissue dielectric constant (dimensionless) and TIF is the tissue indentation force in mN. TDC_CVI and TIF_CVI are their corresponding coefficients of variation (CV) expressed as a percentage. CVI is based on the average of multiple individual measurements for each of the 30 patients. Asterix (*) denotes significantly different between medial and lateral sites at a p-value <0.05 and ** denotes leg difference at a p-value <0.01.

measured at lateral and medial standard leg sites. In Figure 2, the absence of a correlation between TDC and TIF is visually observed and quantified by the regression equation for the lateral leg site shown in Figure 2A as TDC = 46.5 + 0.005 TIF ($r^2 = 0.0078$, $p = 0.664$) and the medial leg site shown in Figure 2B as TDC = 49.1–0.004 TIF ($r^2 = 0.0049$, $p = 0.714$). Contrastingly, as shown (Fig. 3), there was a significant positive correlation between TIF and TDC as measured on the forearm and characterized by the linear regression equation shown in Figure 3 as TDC = 23.7 + 0.089 TIF, $r^2 = 0.196$, $p = 0.014$.

Leg-to-arm TDC values and distributions

Average leg-to-arm TDC ratios (mean ± SD) were similar, whether the leg medial site was used (1.787 ± 0.363) or the lateral site was used (1.751 ± 0.287). Figure 4 shows the distribution of LAR in comparison to the previously determined threshold level of 1.35[21] that is indicated in the figure as the horizontal dashed line. At the medial leg site, 29/30 ratios (96.7%) exceeded the 1.35 threshold, whereas at the lateral site 28/30 ratios (93.3%) exceeded the threshold.

Discussion

Comparison of TDC values

Absolute TDC values to the depth measured on the forearm in the present study (28.0 ± 4.0) were similar to those reported (28.0 ± 2.4) in nonedematous forearms of 40 young healthy women (23.8 ± 2.7 years),[38] and reported (28.9 ± 4.1) in nonedematous forearms of 30 mature women (58.0 ± 12.0 years).[21] This suggests that the presence of lower extremity edematous or lymphedematous conditions has not altered the upper extremity skin water state and forearm values are representative of a normal hydration state in the presently studied group. Lower extremity TDC values on healthy nonedematous legs have been reported for 30 mature women as 29.4 ± 4.7 on medial calf at a site similar to that herein measured.[21]

Thus, the lower extremity values for the presently evaluated edematous group are notably greater than normally measured, with a medial leg TDC value of 48.3 ± 8.3, which is significantly greater than TDC values of the previously measured healthy group ($p < 0.05$).

Comparison of TIF values

Contrastingly TIF values measured on anterior forearms in a group of 30 mature women (56.4 ± 7.6 years) yielded TIF values (43.8 ± 14.9 mN),[39] which were closer to those presently measured. Overall, the present forearm TIF values are consistent with most previously reported values. Fewer studies have provided TIF data on legs. One study estimated the average TIF in patients with cancer-related lower extremity lymphedema by determining TIF as the average of measurements at 20 systematically arranged points on the leg.[24] These values ranged from 71.1 ± 8.7 mN for stage I lymphedema to 160.5 ± 30.4 mN for stage III.

A similar study, in which 56 women with lower extremity lymphedema were evaluated, indicated a leg average TIF value of 160 ± 70 mN in lymphedematous legs compared to 90 ± 30 mN in contralateral apparently nonaffected legs.[25] These prior values are somewhat less than herein measured at

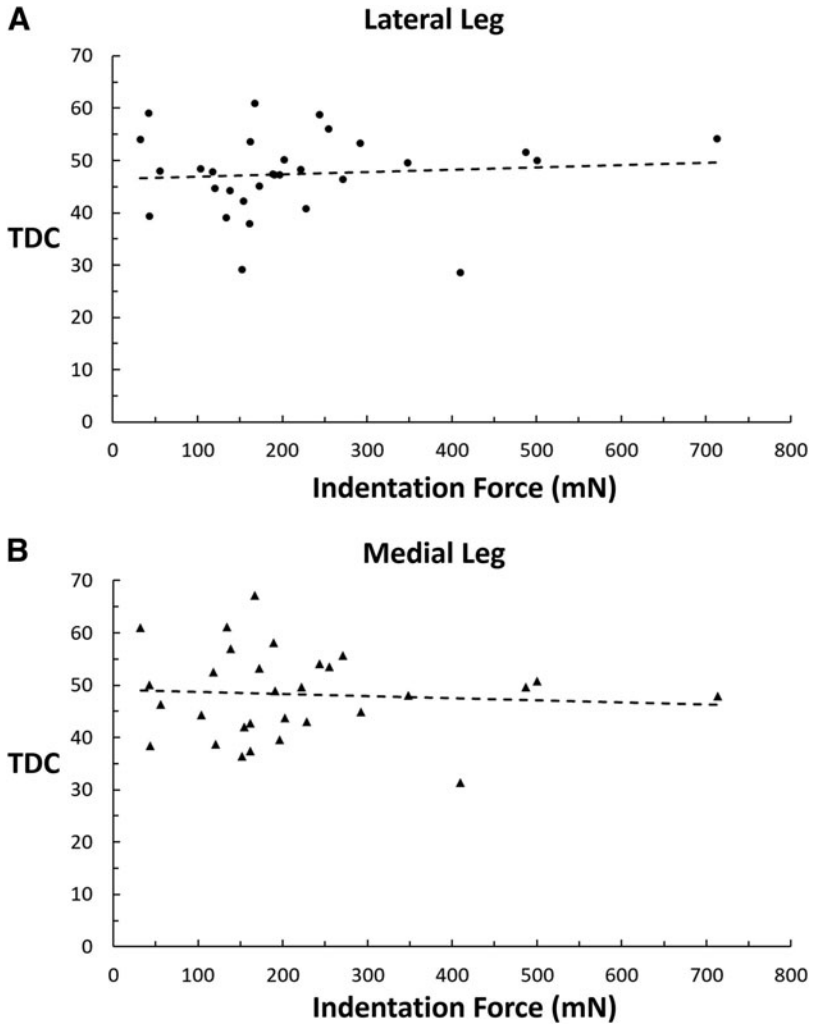

FIG. 2. TDC—Indentation Force Relationships on Leg. In **(A)** Individual paired TDC–TIF values measured on the target leg at the lateral site along with its calculated regression line (*dashed*). In **(B)** is the corresponding data as measured on the medial leg site. As may be visualized by the near horizontal regression lines, there is no significant correlation between the two parameters at either site. The corresponding regression equations are given in the text. TIF, tissue indentation force.

a single standardized lateral leg sites, but are not directly comparable since the prior values include both upper and lower leg measurements.

Coefficient of variation among measurements

The mean CVI of TDC measurements expressed as percentage was less at the standard medial site than at the lateral site (3.38 ± 2.3 vs. 5.15 ± 4.9) and least at the forearm (2.7 ± 2.6). Contrastingly, the overall mean CVI of the five TIF measurements at the leg lateral site was 17.6 ± 10.4 and somewhat less at the forearm site (14.0 ± 8.6). The CVI of the present TDC measurements are consistent with previously reported measurements on forearm and legs.[40] Although there are data in the literature regarding variability of sequentially obtained five value TIF averages,[24,25,36,41–43] this is the first report of the coefficient of variation of sequentially obtained individual values. These values provide an estimate of device measurement precision on lymphedematous lower extremities potentially useful in future assessment comparisons.

TDC–TIF dependence

A new finding based on the present paired TDC–TIF measurements reveals the absence of an identifiable relationship between TDC and TIF in the lymphedematous legs evaluated. Contrastingly, a significant positive correlation between these two parameters was found on nonedematous forearms. Apart from the differences in anatomical locations, one possible functional explanation for these findings may relate to the role of water and tissue properties of the two sites since both water content and tissue properties affect TIF. Evaluation of nonedematous arms will likely require proportionately greater force to indent to a given depth for small differences in water content due to water's low compressibility.

However, at already much higher water content levels, as was present to varying degrees with the edematous legs evaluated, the impact of incremental water content changes on required indention force is likely diminished. A test of this concept would be if the positive correlation between TIF and TDC herein observed in nonlymphedematous arms would be diminished or lost in breast cancer-related arm

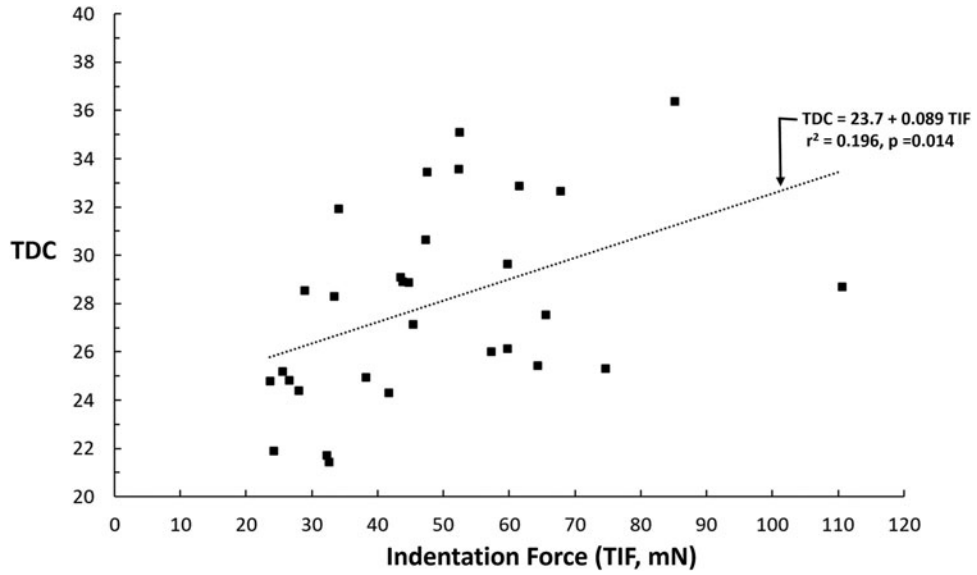

FIG. 3. TDC—Indentation Force Relationships on Forearm. Individual paired TDC–TIF values measured on the forearm and the calculated regression line (*dotted*) with the associated linear regression equation shown in the figure demonstrating a significant positive correlation between TDC and TIF.

lymphedema. Such a comparison study could be conducted with women who have various degrees of upper extremity unilateral lymphedema. Such a study would seem warranted to clarify the issue.

Leg-to-arm TDC ratios

As already noted, prior measurements of leg-to-arm TDC ratios of a group of 60 healthy subjects indicated that all ratios were less than a threshold value of 1.35.[21] In the same study six patients with congestive heart failure (CHF) were also measured and it was found for this small group, all but one had ratios greater than 1.35. The present results extend confidence in this threshold as an indicator parameter of the presence of LELE.

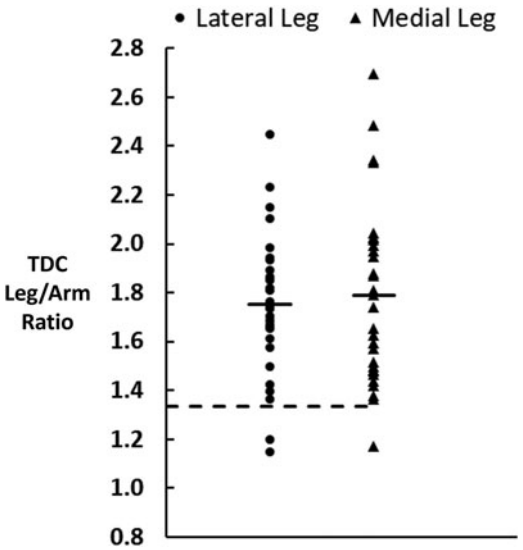

FIG. 4. Leg-to-arm TDC Ratios. Individual LAR are calculated using the lateral leg measurements (*circles*) and using the medial leg measurements (*triangles*). The short solid horizontal lines represent the means and the longer *dashed line* represents an LAR proposed threshold value of 1.35. Based on the medial leg data 29/30 ratios (96.7%) exceeded the 1.35 threshold whereas using the lateral site data 28/30 ratios (93.3%) exceeded the threshold. LAR, leg-to-arm ratios.

Study limitations

There are several limitations to the present study that should be considered. The study included patients with diagnoses of lymphedema or edema. Thus, definitive statements regarding specific conditions cannot be fairly made. Further studies in which each of these conditions is dealt with separately would seem warranted to provide additional specificity. However, it can be stated that the proposed threshold is indicative of lower extremity excess fluid accumulation.

Another possible limitation is that only females were included. This was a practical limitation dictated by the nature of patient availability. However, one implication of this is that lower extremity lymphedematous conditions related to prostate surgery or radiation were excluded from evaluation. Another potential limitation was that TDC and TIF data sets were obtained on a given day with no attempt to repeat the measurements on subsequent days. Thus, the data represent a snap-shot view and further test–retest studies may be warranted to confirm the stability of the present findings.

Conclusion

In conclusion, the present findings suggest the following.

(1) In patients with LELE, TDC values are elevated compared to normal, and average TDC values are similar as measured on medial or lateral standardized sites.
(2) The leg to forearm TDC ratios determined using either medial or lateral sites are similar to each other and have values consistent with a lymphedema threshold of 1.35 as previously reported.

(3) In edematous legs of the type evaluated herein, there is no apparent relationship between TDC values and indentation force.

Authors' Contributions

All authors contributed to and reviewed this article and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

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