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TISSUE DIELECTRIC CONSTANT (TDC) MEASUREMENTS AS A MEANS OF CHARACTERIZING LOCALIZED TISSUE WATER IN ARMS OF WOMEN WITH AND WITHOUT BREAST CANCER TREATMENT RELATED LYMPHEDEMA

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ABSTRACT

Quantitative measurements to detect lymphedema early in persons at-risk for breast cancer (BC) treatment-related lymphedema (BCRL) can aid clinical evaluations. Since BCRL may be initially manifest in skin and subcutis, the earliest changes might best be detected via local tissue water (LTW) measurements that are specifically sensitive to such changes. Tissue dielectric constant (TDC) measurements, which are sensitive to skin-to-fat tissue water, may be useful for this purpose. TDC differences between lymphedematous and non-lymphedematous tissue has not been fully characterized. Thus we measured TDC values (2.5 mm depth) in forearms of three groups of women (N=80/group): 1) healthy with no BC (NOBC), 2) with BC but prior to surgery, and 3) with unilateral lymphedema (LE). TDC values for all arms except LE affected arms were not significantly different ranging between 24.8 ± 3.3 to 26.8 ± 4.9 and were significantly less (p<0.001) as compared to 42.9 ± 8.2 for LE affected arms. Arm TDC ratios, dominant/non-dominant for NOBC, were 1.001 ± 0.050 and at-risk/contralateral for BC were 0.998 ± 0.082 with both significantly less (p<0.001) than LE group affected/control arm ratios (1.663 ± 0.321). These results show that BC per se does not significantly change arm LTW and that the presence of BCRL does not significantly change LTW of non-affected arms. Further, based on 3 standard deviations of measured arm ratios, our data demonstrates that an at-risk arm/contralateral arm TDC ratio of 1.2 and above could be a possible threshold to detect pre-clinical lymphedema. Further prospective measurement trial are needed to confirm this value.

Keywords: lymphedema, tissue dielectric constant, skin water, breast cancer, lymphedema detection

Quantitative measurements for early detection of lymphedema in persons at-risk for breast cancer treatment-related lymphedema (BCRL) can be an aid to standard clinical evaluations. To be useful in a clinical setting, such measurements and associated devices should optimally be noninvasive and readily implemented in an ordinarily busy and time pressured environment. Potential candidates that have been used or may be suitable for routine use include various arm metrics including arm girth and arm volumes (1-12) based on manual or automated methods and arm bioimpedance measured at single or multiple frequencies (13-24).

However, since BCRL may be initially manifest as subtle small increases in dermal and hypodermal fluids (25-28), optimum detection of these earliest changes might require localized measurements of skin-to-fat tissue water changes. Such changes are evaluable by measuring the local tissue dielectric constant (TDC) since TDC values are directly related to tissue water content (29-35). A feature of the TDC method, not present in other methods, is its ability to measure at almost any body site in which changes in tissue water are of clinical interest. Although the TDC method has been applied in a variety of ways to assess tissue fluid and its change (36-48), the needed comprehensive characterizations of expected differences between lymphedematous and non-lymphedematous tissue has not been fully established. Thus, our main goal was to provide such a characterization by comparing paired forearm TDC values and arm-to- arm TDC ratios, measured to 2.5 mm depth, in three groups of women: 1) healthy women with no breast cancer (NOBC), 2) women recently diagnosed with breast cancer (BC) but prior to their surgery, and 3) women with clinically diagnosed overt unilateral lymphedema (LE).

METHODS

Subjects

A total of 240 women, equally divided into three groups of 80, were evaluated after signing a University Institutional Review Board approved informed consent. The groups consisted of 1) healthy women with no breast cancer (group NOBC), 2) women recently diagnosed with breast cancer but prior to their surgery (group BC), and 3) women with unilateral BCRL (group LE). Entry requirements for the BC group were that they had recently (within one month) been diagnosed with breast cancer and were awaiting surgery. These patients were referred by their surgeon for a pre-surgery evaluation. Entry requirements for the LE group were that they had unilateral lymphedema and had been referred for lymphedema therapy. Entry requirements for the NOBC group were that they had no history of breast cancer, had no previous surgery or serious trauma to either arm, and were in self-reported good health. Pertinent features of the three study groups are shown in *Table 1.* From data available for the LE group, the average number of axilla nodes removed at surgery was (mean ± SD) 13.3 ± 9.7 with a range of 3-27 and the average reported duration of the lymphedema was 74.6 ± 91.1 months with a range of 2-433 months. As may be seen from the *Table 1*, ages and BMI of the groups were significantly different from each other in the order NOBC < BC < LE ($p<0.001$) indicating a wide representative range of subject features.

Tissue Dielectric Constant (TDC) Measurement Device

TDC was measured with the MoistureMeter-D (Delfin Technologies Ltd, Kuopio, Finland). The skin-contacting part of the device consists of a cylindrical probe that is connected to a control unit that displays the tissue dielectric constant when the probe is placed in contact with the skin. The probe itself acts as an open-ended coaxial transmission line (29,49) and the principle of operation has been well described (29,31,34,49,50). In brief, a 300 MHz signal, generated within the control unit, is transmitted to the tissue via the probe in contact with the skin. The portion of the incident electromagnetic wave reflected from the tissue depends on the tissue's dielectric constant, which itself depends on the amount of free and bound water in the tissue volume through which the wave passes. Reflected wave information is processed in the control unit and the dielectric constant is displayed. For reference, pure water has a value of about 78 and the display scale range is 1 to 80. The effective measurement depth depends

TABLE 1 Study Group Features			
	Group NOBC – Healthy	Group BC - Breast Cancer	Group LE - Lymphedema
Number of Subjects (N)	80	80	80
Age (years)	33.4 ± 13.6 [18-71]	59.4 ± 13.0 [28-82]	70.4 ± 12.1 [42-97]
BMI (Kg/m^2)	24.7 ± 5.2 [14.7-37.9]	28.4 ± 7.2 [17.8-48.1]	30.0 ± 6.2 [20.5-53.3]
BMI < 25 Kg/m^2 - Normal	49/80 (61.3%)	31/80 (38.8%)	11/80 (13.8%)
BMI 25-29.9 Kg/m^2 - Overweight	18/80 (22.5%)	25/80 (31.2%)	37/80 (46.2%)
BMI ≥ 30 Kg/m^2 - Obese	13/80 (16.2%)	24/80 (30.0%)	32/80 (40.0%)
Right Arm Dominant	61/80 (92.4%)	49/80 (74.2%)	50/80 (75.8%)
Dominant Arm is At-Risk or Affected		39/80 (48.8%)	45/80 (56.2%)

Values are mean ± SD where applicable with [ ] indicating range; BMI is body mass index. Group ages and BMI are significantly different in the order NOBC < BC < LE (p<0.001). At-Risk arm for breast cancer (BC) and lymphedema (LE) groups correspond to the at-risk and affected sides respectively.

on the probe dimensions, with larger spacing between inner and outer conductors corresponding to greater penetration depths. Probes are available to measure to effective depths of 0.5, 1.5, 2.5 and 5.0 mm, but this study utilized only the 2.5 mm depth probe so as to include the epidermis, the dermis, and part of the hypodermis of the target forearm skin. This probe has an outside diameter of 23 mm and inner-to-outer conductor spacing of 5 mm.

TDC Measurement Procedure

TDC measurements began after a subject was lying supine for 10 minutes on a padded examination table with arms at her side and hands positioned with palms up thereby exposing the anterior surface of both forearms. A standardized measurement site located 6 cm distal to the antecubital fossa along the forearm midline was marked with a dot to serve as a reference center point for probe placement. A single TDC measurement was obtained by placing the probe in contact with the skin of one arm and held in position using gentle pressure. After about 10 seconds an audible signal indicated completion of the measurement. The probe was then used to make a measurement on the other arm to complete a measurement pair. This process was continued to obtain triplicate measurement pairs. Alternating between arm sides was used as a way to help obtain paired values as close in time as possible. For each arm, the three measurements were averaged and used to characterize the arm site average TDC value.

Arm Girth Measurements

After the TDC measurements, circumferences (girth) of the arm at the reference center point were measured using a calibrated Gulick-type spring-loaded tape measure with a tension gauge to help insure uniform measurements.

Data Reduction and Analysis

BC group paired-arms were designated as at-risk and contralateral and LE group paired-arms were designated as affected and contralateral. NOBC group paired-arms were designated as dominant and non-dominant

TABLE 2
TDC and Girth Results

	Tissue Dielectric Constant (TDC)			Forearm Girth (cm)		
Group[a]	Affected (A) Side	Control (C) Side[b]	TDC Ratio (A/C)	Affected (A) Side	Control (C) Side[b]	Girth Ratio (A/C)
NOBC	26.8±4.9	26.4±4.7	1.001±0.050	23.3±2.4	23.4±2.4	1.013±0.033
BC	24.8±3.3	24.9±3.8	0.998±0.082	24.2±2.6	24.3±2.6	0.997±0.034
LE	42.9±8.2**	26.0±4.0	1.663±0.319	28.8±4.2**	24.2±3.3	1.216±0.152[§]

[a]For breast cancer (BC) and lymphedema (LE) groups affected (A) sides refers to at-risk arms and lymphedema arms respectively; control sides are the contralateral arms. For the healthy group (NOBC) side A corresponds to the dominant arm and side C corresponds to the non-dominant arm. [b]Control side TDC and girth values show no significant difference among groups.
** TDC and girth values of LE group affected arms were significantly greater than for BC or NOBC groups (p<0.001). For BC and NOBC groups, TDC and girth values were insignificantly different between paired-arms and between groups yielding similar A/C ratios. [§]A/C ratios for the LE group were significantly greater than for either the BC or NOBC groups (p<0.001). Values reported are mean ± SD.

depending on the subject's self report. Paired arm mean values ± SD and paired-arm ratios were determined as dominant/non- dominant, at-risk/contralateral, and affected/contralateral for NOBC, BC, and LE groups, respectively. Overall differences among the three groups with respect to each arm-side TDC or girth value and the TDC or girth arm-to-arm ratio was tested for using an analysis of variance model (ANOVA) with Bonferroni post hoc comparison tests. Differences between arm side TDC and girth values were subsequently tested for using paired t-tests. In all cases, a p-value <0.05 was taken as significant. Tests for correlations among parameters were done using Pearson coefficients. All statistical analyses were done using SPSS version 13.0 (SPSS Inc., 233 S. Wacker Drive, Chicago, IL).

RESULTS

Arm Girths

Arm girth differences between sides and between groups were insignificant for both the NOBC and BC groups, whereas, as was to be expected, the girth difference between sides for the LE group was highly significant (p<0.001) as summarized in (*Table 2*). Although the LE group arm-to-arm girth difference was highly significant, the LE contralateral arm girth was insignificantly different from the girth of any arm of the NOBC or BC group. Girth ratios, assessed as the at-risk to the contralateral arm in the BC group (0.997 ± 0.034), was insignificantly different than the dominant/non-dominant ratio for the NOBC group (1.013 ± 0.033) with both ratios being significantly less than the affected/contralateral ratio of the LE group (1.216 ± 0.152, p<0.001).

TDC and Local Tissue Water

As with the girth findings, arm TDC differences between sides and between groups were insignificant for both the NOBC and BC groups, whereas inter-arm TDC differences for the LE group were highly significant (p<0.001) as summarized in *Table 2*. Although the LE group inter-arm TDC difference was highly significant, the TDC value of the LE contralateral arm was insignificantly different from TDC values measured on all arms of the NOBC or BC groups. TDC ratios, assessed as at-risk to contralateral arms in the BC group (0.998 ± 0.080, range 0.838-1.159), were insignificantly different than dominant/non-dominant arm ratios for the NOBC group (1.001 ± 0.050, range 0.871- 1.158) with both of these TDC inter-arm ratios significantly less than the affected/contralateral TDC ratio of the LE group (1.663 ± 0.319, $p<0.001$, range 1.176-2.438). Girth ratios compared to TDC ratios did not significantly differ between NOBC or BG groups but the TDC ratio was significantly ($p<0.001$) greater than the girth ratio for the LE group.

Correlations of Parameters

As might have been anticipated, there was a strong positive correlation ($p<0.001$) between paired-arm TDC values and paired-arm girths within groups. Group NOBC correlation coefficients for TDC and girth were respectively 0.958 and 0.942. However, there was no significant correlation between TDC and girth either for absolute values or for arm-to-arm ratios. Correlation patterns of the BC group were similar to the NOBC group with correlation coefficients for TDC and girth being respectively 0.843 and 0.948 with no other significant correlations among parameters. For the LE group, these correlations were also significant ($p<0.001$) but with smaller correlation coefficients being for TDC and girth 0.463 and 0.790, respectively.

DISCUSSION

Measuring local skin-to-fat tissue water based on the tissue dielectric constant (36,51-53) represents an adjunctive approach to better characterize lymphedema and to potentially provide a method for an earlier detection of latent or incipient lymphedema. The TDC method differs from limb volume (1,3,4,7,8) and bioimpedance methods (22,23,54,55) in that with a 2.5 mm measurement depth as used here, it only interrogates skin and subcutaneous tissue compartments in which some of the earliest changes are likely to occur (27,28). Since it is a local measurement, it can be used at almost any anatomical site that is at-risk for lymphedema development. Although differences in tissue water between frankly lymphedematous and contralateral non-affected limbs have been determined by TDC measurements (36,39), differentials between limbs of healthy persons and persons with breast cancer but without lymphedema have only been partially characterized (56). Thus, a major goal of this study was to characterize forearm local tissue water parameters, as assessed by TDC measurement, among women without breast cancer (NOBC) and with breast cancer (BC) in comparison with women with breast cancer treatment related lymphedema (LE). An important major intended component of this characterization was the assessment of the range of TDC variability among groups with the thought of devising suitable reference ranges and TDC thresholds potentially useful to detect early lymphedema development.

One main result shows that, except for patients with lymphedema (the LE group), absolute TDC values of arms are similar and insignificantly different from each other. This includes all arms of the BC and NOBC groups and the contralateral arm of the LE group. The ratio of affected to contralateral arm TDC values, expressed as mean ± SD for the 80 evaluated women with lymphedema (1.663 ± 0.319) was much greater than the near unity ratios found in women in the BC group (0.998 ± 0.082) or the NOBC group (1.001 ± 0.050). The closeness of the TDC values of all arms for the BC and NOBC groups strongly suggests that breast cancer in the BC group did not significantly affect local tissue water in either arm. The TDC findings also indicate that lymphedema presence in the LE group did not significantly affect local tissue water in the contralateral arm of these women.

Because the at-risk arm may be the patient's dominant or non-dominant arm (*Table 1*), it is useful to characterize the dominant/non-dominant TDC ratio with as large a data set as meaningfully available. Since the present analyses indicated no

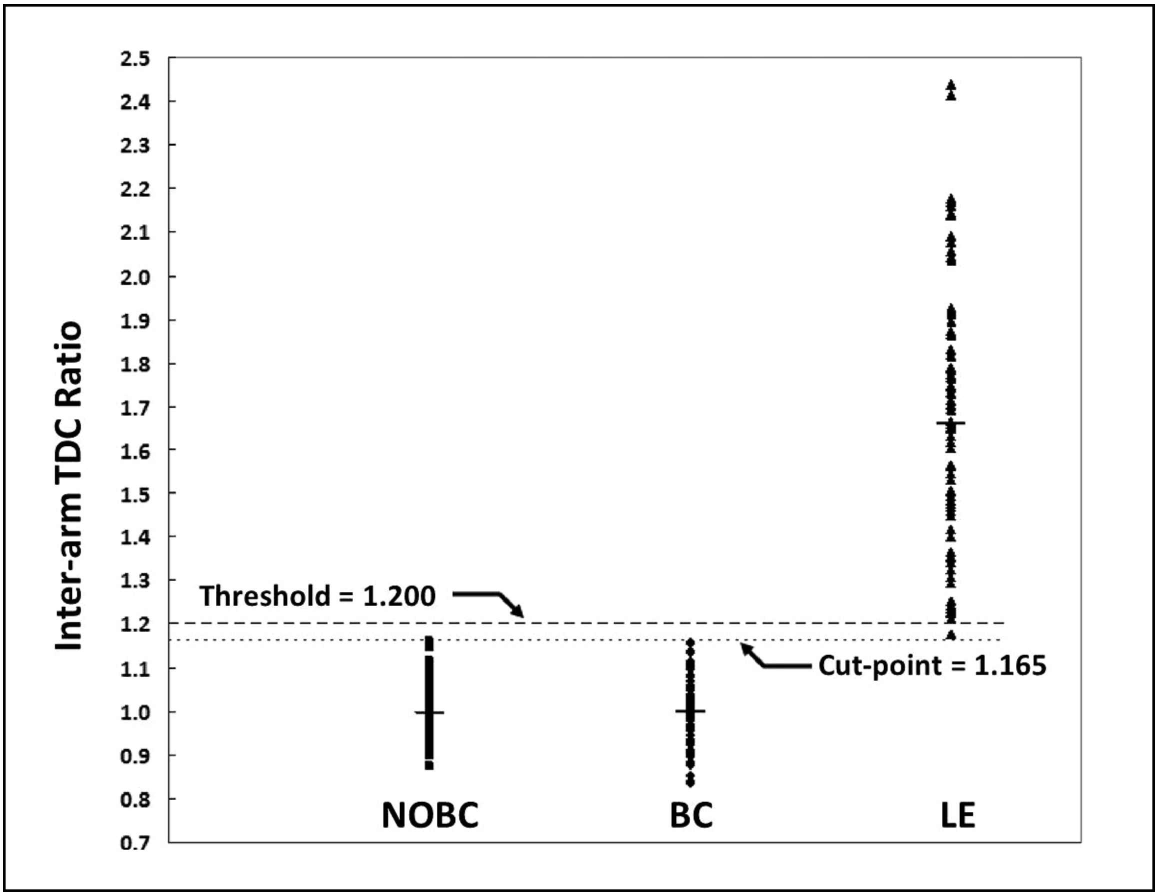

Fig. 1. Distribution of Arm-to-Arm TDC Ratios. NOBC, BC, and LE correspond to groups with no breast cancer, breast cancer, and lymphedema respectively each with N = 80 subjects. BC ratios were calculated as at-risk arm/contralateral, LE ratios were calculated as affected arm/contralateral, and NOBC ratios were calculated as dominant arm/non-dominant. Short horizontal bar on each plot indicates group average. NOBC and BC ratios were insignificantly different from each other and both were significantly less than for the LE group (p<0.001). The threshold line indicates the mean dominant/non-dominant ratio for all non-lymphedematous subjects (N=160) plus 3SD. The cut-point line indicates the TDC ratio that is less than observed for any patient with lymphedema and is greater than any observed for non-lymphedematous persons.

difference between BC and NOBC groups with respect to arm-to-arm TDC values, we combined these groups (N=160) to determine the combined dominant/non-dominant TDC ratio of 0.995 ± 0.067 (range 0.838 - 1.159). Corresponding girth ratios were 1.014 ± 0.032 (range 0.829 - 1.084). This combined data set provides values from a wide age range (18-82 years) and a wide BMI range (14.7 - 48.1 Kg/m^2) that can be used to estimate the effects of age and BMI on TDC and girth ratios.

For this combined data set, correlation analyses revealed a near zero Pearson correlation coefficient between age or BMI and TDC or girth ratios. This indicates that age and BMI are not factors of significant relevance with respect to dominant/non-dominant arm ratios. The local TDC and girth ratios here obtained may be compared with whole arm ratios obtained via bioimpedance measurements for a group of 60 control subjects (23) where a dominant to non-dominant ratio of 0.964 ± 0.034 was obtained and for a group of 32 subjects in which a dominant to non-dominant ratio was 1.024 (21). It should be noted that with impedance measurements higher values of arm water yield lower impedance values.

As previously stated, one of the goals of this study was to provide a reference data set from which estimates of deviations in local TDC values from normality might be detected early in the process of lymphedema development. One methodological approach is to define a threshold for sub-clinical lymphedema as a value that equals or exceeds the reference mean plus some multiple of the reference standard deviation. This approach has been utilized when whole arm impedance values were to be used as the assessment parameter (13,23) and a threshold inter-arm impedance ratio of between 1.106 to 1.134 was determined depending on hand dominance (13). Applying the same conservative criteria to the present TDC data, using the standard deviation of the 160 dominant to non- dominant TDC ratios indicates a 3SD value of 0.201 that when added to the mean TDC ratio yields a threshold value of 1.196 which we may round up to 1.200. It is noteworthy that all subjects within our non-lymphedematous sample population (combined BC and NOBC groups) had an inter-arm TDC ratio less than this threshold with the overall arm- to-arm TDC distributions shown in *Fig. 1*. For the LE group, 78 of 80 women (97.5%) had TDC ratios exceeding this threshold. This implies that had the threshold criteria been applied, 2/80 (2.5%) of the group that actually had lymphedema would not have been detected with this method. An alternate approach to arriving at suitable cut-point criteria is to determine if there is a TDC ratio that is less than observed for any patient with lymphedema and is greater than observed for any non-lymphedematous patient. For the present evaluated population a value satisfying this criterion is 1.165 and is shown as the small dotted line in *Fig. 1*.

In summary, the present results provide reference TDC values derived from a large group of female forearms and also provide a practical at-risk/contralateral arm TDC ratio of 1.200 and above that could be useful to indicate pre-clinical or impending lymphedema if measured in women who have previously been surgically treated for breast cancer. It is emphasized, however, that these theoretically calculated TDC thresholds have not as yet been prospectively substantiated and should conservatively be viewed as referenced-based targets for future prospective research investigations.

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