

TISSUE DIELECTRIC CONSTANT (TDC) AS AN INDEX OF SKIN WATER IN WOMEN WITH AND WITHOUT BREAST CANCER: UPPER LIMB ASSESSMENT VIA A SELF-CONTAINED COMPACT MEASUREMENT DEVICE

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ABSTRACT

Previous work showed tissue dielectric constant (TDC) measurements at 300 MHz useful to evaluate local skin water and then a hand-held compact version provided values similar to the original multi-probe system when assessed in healthy subjects. Our current goals were to use the compact portable device to determine: 1) its utility in assessing age-related differences between younger healthy women vs. women with breast cancer (BC); 2) upper-arm site differences in women with BC and 3) its utility and limitations of a single measurement vs. averaging triplicate measurements. A total of 84 women were included; 42 were young (24.0 ± 2.4 years) self-described healthy women (group A) and 42 were older (65.5 ± 1.6 years) women with recently diagnosed BC who were awaiting surgery (group B). In both groups TDC values were assessed on the anterior forearm and in group B at the hand, forearm and biceps with all measurements bilateral and in triplicate. Results showed the following. 1) Forearm TDC values are similar for younger and older groups with no significant differences (NSD) between groups or between dominant and non-dominant sides or inter-arm ratios. 2) Hand TDC values are about 21% greater than forearm and biceps values but inter-arm ratios (at-risk/contralateral) are NSD among sites

with values for hand, forearm and biceps of 1.027 ± 0.180 , 0.997 ± 0.066 and 1.010 ± 0.075 respectively. 3) Based on limits of agreement analyses, single TDC measurements are adequate for most forearm and biceps evaluations but multiple measurements are likely needed for hand measurements. 4) Theoretical detection thresholds for unilateral lymphedema using a 3SD limit of inter-arm ratios are 1.57, 1.20 and 1.24 for hand, forearm and biceps. These ratios indicate likely useful forearm and biceps thresholds but a less useful ratio at the hand due primarily to the large variance in hand TDC values among patients.

Keywords: edema, lymphedema, dielectric constant, hand-held device, lymphedema measurement, skin

Previous work has shown the utility of tissue dielectric constant (TDC) measurements made at 300 MHz to evaluate local skin water (1-4) using the concentric transmission line measurement technique (5-8). A multi-probe system, consisting of separate probes connected to a control unit provided different sized probes that allowed for skin depth measurements ranging from 0.5 mm to 5.0 mm (4,9). More recently a modified version in the form of a compact hand-held device that measures to a single

depth was evaluated and shown to yield TDC values between those obtained by probes measuring to effective depths of 1.5 mm to 2.5 mm (10). Because of its small size, portability and other features, the compact version is probably more conveniently used as a clinical tool to routinely quantitatively assess skin tissue water in edematous and lymphedematous conditions. However, because of its limited initial use and published data, there are several questions regarding its applicability and potential limitations that need to be addressed.

One question relates to how age-related differences in TDC values are affected. Prior work, using different depth-measuring probes, has shown that TDC values at 0.5 mm and 1.5 mm depths were greater in older women as compared to younger but that no such difference was present when measured to a depth of 2.5 mm (11). Since the effective measurement depth of the compact device is between these limits (10), it is unknown how age-related differences will be characterized. Thus one of the aims of this study is to evaluate compact-TDC values between widely different age groups.

A second question relates to variability of measured TDC values among anatomical sites. Prior work has shown significant TDC differences between anatomical sites that are of interest in the assessment of lymphedema including forearm, biceps, axilla and chest (12,13). However, since site differences have only been evaluated to a depth of 2.5 mm it is unclear what differences would be present among sites for a lesser depth. Further there have been no reported TDC measurements in the hand, an anatomical site often involved in lymphedematous states. Thus a second aim was to characterize the variability of TDC values among hand, forearm and biceps in women with breast cancer.

A final question that impacts the potential clinical utility of TDC measurements is the time factor. This relates to the number of physical replications needed to suitably characterize the tissue being evaluated.

The more replications needed, the longer the needed time. Prior work has considered this question using the multi-probe system and provided guidance as to the suitability of a single measurement compared to averaging multiple measurements (14). A similar analysis is needed for the single depth compact device and is the third aim of this research.

METHODS

Subjects

A total of 84 women were included in this study. Forty two were young self-described healthy adult women (group A) and 42 were older women with recently diagnosed breast cancer who were awaiting surgery (group B). All were evaluated after signing a University Institutional Review Board approved informed consent. Group A women were drawn from 1st and 2nd year medical students and group B women were drawn from patients referred for breast cancer surgery. Entrance requirements for both groups were that they be at least 18 years of age and have no history of serious arm trauma and no self-reported or visual evidence of any abnormal arm skin condition at the time of evaluation. Group B had the additional requirement of being diagnosed with unilateral breast cancer within two weeks of their participation in this study but prior to their treatment. All participants were advised not to use any form of cream or lotions on their arms on the day of their evaluation. Ages (mean \pm SD) for group A were: 24.0 \pm 2.4 years (range 18-29) years and for group B was 65.5 \pm 1.6 years (range 43-87 years). As shown in *Table 1*, groups A vs. B differed significantly with respect to body mass index (BMI) with group B significantly greater than group A ($p < 0.001$). For group A, 7.5% were underweight (BMI < 18.5 Kg/m²), 65% were classified as having a normal BMI (18.5 Kg/m² - 24.9 Kg/m²), 15% were overweight (BMI 25-29.9 Kg/m²) and

TABLE 1
Age-Related Group Comparisons

	Group A	Group B	
N	42	42	p-value
Age (years)	24.0 ± 2.4 (18 - 29)	65.5 ± 1.6 (43 - 87)	0.0001
BMI (Kg/m ²)	23.5 ± 4.6 (16.8 – 37.0)	28.0 ± 5.2 (18.0 – 41.0)	0.001
TDC _{AVG}	28.5 ± 3.5 (22.3 - 43.0)	29.2 ± 3.5 (22.6- 35.5)	0.332
TDC _{RATIO}	0.999 ± 0.050 (0.895 - 1.176)	0.989 ± 0.068 (0.785 - 1.122)	0.480
Girth _{AVG} (cm)	23.1 ± 2.3 (18.6 – 28.0)	23.3 ± 2.9 (17.3 – 28.0)	0.844
Girth _{RATIO}	1.017 ± 0.027	1.020 ± 0.026	0.643
Data are mean ± SD and (range) for younger (group A) and older (group B) female groups. BMI = body mass index, TDC _{AVG} and Girth _{AVG} = average of dominant and non-dominant forearm, TDC _{RATIO} and Girth _{RATIO} = inter-arm TDC ratio (dominant / non-dominant)			

12.5% were obese (BMI ≥ 30 Kg/m²). Contrastingly for group B, 2.5% were underweight, 20% were normal, 50% were overweight and 27.5% were obese. In group A the right hand was the self-reported dominant hand in 78% of subjects and in group B the right hand was the self-reported dominant arm in 93% of subjects. The arm at-risk for lymphedema (the cancer side) was the self-reported dominant side in 67.5 % of group B subjects.

TDC Measurement Device

The device used to measure TDC was the MoistureMeterD compact (MMDC) manufactured by Delfin Technologies Ltd, Kuopio, Finland. This device is a recently developed hand-held version of the multi-probe system, made by the same company, that has been extensively used to measure TDC as an index of skin-to-fat tissue water (1,15,16). The features of the compact device in comparison to the original multi-probe system have recently been evaluated and compared (10). The underlying physics and

principle of operation of the basic method have been well described (5,17-19). In brief, a 300 MHz signal is generated and transmitted to the tissue by the device that acts like an open ended coaxial transmission line. A part of the incident electromagnetic energy is reflected in an amount that depends on the dielectric constant of the tissue, which itself depends on the amount of free and bound water in the tissue volume. Reflected energy information is processed within the device and the value of the dielectric constant determined. For reference, pure water at a temperature of 34°C has a dielectric constant value of about 76. The compact device used in the present study has a readout that does not directly give TDC values. Instead it provides a digital readout that is the local tissue water percentage (LTW%), which according to the manufacturer is calculated from the TDC value according to the following equation $LTW(\%) = 100\% \times (TDC - 1)/77.5$. However, in this paper we report only the actually measured parameter, TDC, to facilitate convenient and direct comparisons between TDC values in the literature. If

desired, conversion from a TDC value to estimated percentage water can be done using the above equation in reverse (16). The effective measurement depth of this compact device, which is the depth at which the incident energy falls to about 2/3 of its surface value, has been shown to lie between values obtained from the 1.5 mm and 2.5 mm depths of the multi-probe system (10).

TDC Measurement Procedure

Measurements were done with subjects seated and were started after a 10 minute acclimation rest interval. In both groups TDC measurements were made at standardized sites on the anterior part of both forearms along the midline located 6 cm distal to the antecubital crease. These target measurement sites were marked with dot using a surgical pen to serve as a reference center point for probe placement. In addition, for group B subjects their hand and biceps sites were also marked and measured. The hand site was on the hand dorsum between the thumb and index finger. The anterior biceps site was 8 cm proximal to the antecubital crease. A single measurement was obtained at each site by placing the probe in contact with the skin and held in position using gentle pressure. The compact device has an incorporated pressure sensor and display that allows for a uniform pressure to be applied for multiple readings and among subjects. After about 10 seconds an audible signal indicates measurement completion. TDC measurements were done in triplicate at all sites. All TDC measurements in group A were made by the same investigator (H.N.M.) and all TDC measurements in group B were made by the same investigator (L.L.). Each investigator had substantial experience in TDC measurements. TDC measurement differences between measurers was estimated by having them measure TDC in triplicate on both forearms of six test subjects. The average percentage difference \pm SD between investigators was found to be $2.1 \pm 1.3\%$ and

was deemed suitable for having each measure the separate groups for the purpose of this study. After TDC measurements were completed, arm girth at each site was determined using a tape measure pulled to constant tension using a Gulick-type tape measure (Allegro Medical Supplies, Mesa, AZ, USA).

Analysis

Age-related comparisons: The average of triplicate TDC values at each site, denoted as TDC_3 , was used to characterize each site's TDC value. Potential age-related differences in TDC values were tested using an independent T-test. In this test each subject's forearm TDC value was calculated as the average of dominant and non-dominant TDC_3 values and denoted TDC_{AVG} . TDC_{AVG} was used as the TDC parameter to compare younger (group A) vs. older (group B) subjects. Forearm girths ($Girth_{AVG}$) were compared in a similar way. In addition, TDC and girth inter-arm ratios were calculated as the ratio of dominant to non-dominant arm values and denoted as TDC_{RATIO} and $Girth_{RATIO}$ and compared between age-groups.

For group B, inter-arm ratios were also calculated as the ratio (at-risk arm/contralateral arm).

Variations among sites: Comparisons of TDC values among sites (hand, forearm and biceps) for subjects with breast cancer (group B) was done via analysis of variance (ANOVA) using TDC values for at-risk and contralateral arms separately. Post-hoc comparisons to assess differences between sites were done using the Bonferroni adjustment for multiple comparisons.

Average TDC values vs. single TDC value: Differences in TDC values when using the average of triplicate measurements (TDC_3) compared to the first TDC measurement (TDC_1) were based on the absolute difference $\delta = (TDC_1 - TDC_3)$ and on the

TABLE 2
TDC Values: One vs. Average by Site for Group B

	At-Risk Arm					Contralateral Arm				
	TDC ₃	TDC ₁	δ	% δ	p-value	TDC ₃	TDC ₁	δ	% δ	p-value
Hand	*35.2 ± 6.6	*34.8 ± 6.5	-0.4 ± 2.2	-1.0 ± 5.7	0.240	*34.5 ± 6.1	*34.7 ± 5.7	0.2 ± 1.8	1.0 ± 5.4	0.459
Forearm	29.0 ± 3.4	29.0 ± 3.4	0.0 ± 0.7	0.1 ± 2.5	0.829	29.7 ± 3.8	29.7 ± 3.9	0.0 ± 0.6	-0.1 ± 2.0	0.626
Biceps	29.3 ± 5.5	29.3 ± 5.4	0.0 ± 0.5	-0.1 ± 1.7	0.553	29.0 ± 5.4	29.0 ± 5.3	0.0 ± 0.7	0.1 ± 2.9	0.916

Data are mean ± SD and (range) for older female group with breast cancer prior to surgery.
TDC₃ = TDC determined as average of triplicate values; TDC₁ = TDC determined from first TDC measurements
 δ = TDC₁ - TDC₃, % δ = 100(δ /TDC₃), p-value corresponds to significance of δ , * = p<0.001 as compared to forearm and biceps.

percentage difference % δ = 100 (δ /TDC₃). These comparisons were made for the hand, forearm and biceps separately in the older group (group B).

RESULTS

Age Related Differences (Groups A and B)

Except for a greater body mass index (BMI) of the older group (p=0.001) (Table 1) all other measured forearm parameters were similar between groups with the average of dominant and non-dominant TDC values (TDC_{AVG}) between age groups being 2.4% with the older group mean insignificantly greater. The difference in forearm girth at the TDC measurement site (Girth_{AVG}) was also similar between groups with an average difference of less than 1%. There were also no group differences in the inter-arm ratios of either TDC (TDC_{RATIO}) or girth (Girth_{RATIO}). TDC values for dominant vs. non-dominant forearms were not significantly different between arms for group A (28.5 ± 1.9 vs. 28.5 ± 2.1, p = 0.850) or for group B (29.0 ± 3.5 vs 29.4 ± 3.5, p = 0.225). TDC values for corresponding arms were not significantly different between groups for the dominant arm (p = 0.570) or non-dominant arm (p = 0.300).

Variations Among Sites (Group B)

Hand TDC values were found to be significantly greater (p<0.001) than forearm and biceps (Table 2) being about 20%-22% greater than each. These differences were present whether evaluated on the basis of site-averaged values (TDC₃) or based on the first measurement at the site (TDC₁). TDC values at forearm and biceps were similar and not significantly different (Table 2). Differences between forearm and biceps TDC values were 1% on the at-risk arm and 2.4% on the contralateral arm. Inter-arm TDC ratios (at-risk arm/contralateral arm) were found to be similar among all three sites

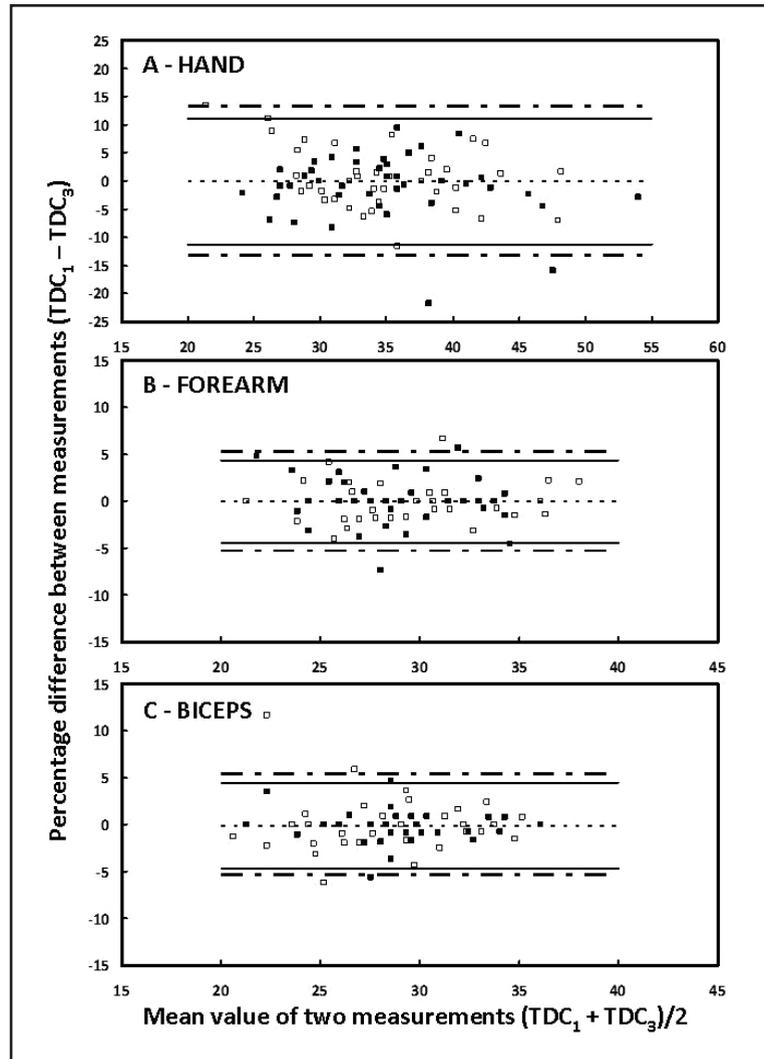


Fig. 1. Bland-Altman plot showing differences between single and averaged tissue dielectric constant measurements for women with breast cancer. The central dashed line is the mean value of the difference, the solid upper and lower lines are located at ± 2 SD from the mean and define the limits of agreement (LOA) and the line (long-dash, short-dash) above and below the LOA are the upper and lower 95% confidence intervals on the LOA. Open squares are data for contralateral arms and closed squares are data for at-risk arms.

being 1.027 ± 0.180 at the hand, 0.997 ± 0.066 at the forearm and 1.010 ± 0.075 at the biceps.

Average TDC Values vs. Single TDC Value (Group B)

Triplicate averaged TDC values (TDC^3) did not significantly differ from first TDC

measurements (TDC_1) on at-risk or contralateral arms at any site (Table 2). Separate analyses show that absolute percentage differences ($1\%|\delta|$) between first TDC measurements and triplicate averages was less than 5% in 96.4% of forearm measurements and in 95.2% of biceps measurements. At the hand, although the average difference

between first TDC value measured and the average was $\pm 1\%$ (Table 2), only 67.9% of measurements were within an absolute difference of 5%. A further useful way of comparing the two methods is that described by limits of agreement (20). For the present data set, the limits of agreement (LOA), which is determined by the mean difference between methods \pm twice the standard deviation of all differences, represents the range for which 95% of values measured by either method are in agreement. The standard graphic summarizing these results is shown in Fig. 1. In the figure, the central dashed line is the mean value of the difference, the solid upper and lower lines are located at ± 2 SD from the mean and define the LOA and the line (long-dash, short-dash) above and below the LOA are the upper and lower 95% confidence intervals on the LOA. For hand, forearm and biceps the LOA range is $+11.1\%$ to -13.3% , $+4.4\%$ to -4.5% and $+4.5\%$ to -4.6% , respectively.

DISCUSSION

The main findings of the present study with regard to TDC measurements that were made with the self-contained compact device may be summarized as follows.

(1) Forearm TDC values are similar for younger and older groups with no significant differences between groups or between dominant and non-dominant sides or inter-arm ratios.

(2) Hand TDC values are about 21% greater than forearm and biceps values but inter-arm ratios are not significantly different among sites.

(3) Single TDC measurements are likely adequate for most forearm and biceps evaluations but multiple measurements would be indicated for hand TDC evaluations.

Age-Related Differences

Prior work that has investigated potential difference in TDC values with age have

provided results suggesting that the presence of age-related differences depends on the tissue depth that is examined. This is probably not completely unexpected since the distribution of water varies with depth as does other tissue components. At effective measurement depths of 0.5 mm and 1.5 mm on forearms of women, TDC values were found to be greater in older women whose average age was similar to those evaluated in the present study (11). The difference found was approximately 18% and 13% at depths of 0.5 and 1.5 mm. Contrastingly, when TDC was measured to a depth of 2.5 mm no age-related difference was found. Similar measurements in males of younger and older sub-groups showed a similar trend in that TDC values were greater in the older group only to a depth of 0.5 mm and here there was an approximate 14% greater value (21). It was concluded that this age-dependent difference could be attributed to a shift in water state from a less mobile to a more mobile state with ageing. The present findings of no detectible difference between age groups would be consistent with the fact that such differences are mostly manifest in the shallowest skin depths (0.5 to 1.5 mm) whereas the present compact device has an effective penetration depth greater than 1.5 mm (10). This would suggest that if a given clinical or research study was majorly involved with assessing age-related changes in skin water based on TDC measurements that consideration should be given to using the multi-probe system capable of shallow depth measurements or using a shallower depth compact device, stated to measure to a depth of 0.5 mm that was not available prior to this study.

TDC Variations among Anatomical Sites

Differences in TDC values among some anatomical sites have been reported for a range of measurement depths on upper and lower extremities (4,9,12). The only known reported measurements at the hand (12), a site of clear relevance in persons with upper

extremity edema or lymphedema, indicate that at this site TDC values obtained at depths of 1.5 and 2.5 mm are significantly greater ($p < 0.001$) than at forearm by $6.7 \pm 10.2\%$ and $19.7 \pm 14.9\%$, respectively. The present data obtained with the compact device, indicates a hand to forearm difference of $18.5 \pm 18.1\%$. This difference is fully consistent with the previously reported value and supports the presence of a significantly greater TDC value on the hand dorsum. Based on the inter-arm ratios at each site (at-risk to contralateral) one can calculate a conservative estimate that would likely represent a sufficient inter-arm difference to detect a unilateral edema or lymphedema (1). Using a three standard deviation threshold a ratio of about 1.2 was determined based on forearm TDC measures to a depth of 2.5 mm (1). Applying the same criteria to the present TDC measurements indicates thresholds for hand, forearm and biceps of 1.57, 1.20, and 1.24 showing similar thresholds for forearm and biceps but a much greater and less useful ratio at the hand due primarily to the large variance in hand TDC values among patients.

Average TDC Values vs. Single TDC Value

Most prior studies in which TDC measurements were made were done so using triplicate repeated measures and then averaged to help reduce measurement variance potentially associated with a single measurement at a given site. This is a useful strategy but increases the time required for each measured site. Further, averaged repeated measurements are only better than one measurement if relevant results are significantly different. Previous work has examined the suitability of single forearm TDC measurements in comparison to the average of multiple measurements and provided guidance as to its adequacy based on acceptable limits (14,22). Measurements to various depths indicated one vs. the average of multiple TDC differed by less than ± 1 TDC unit in both lymphedematous and

non-lymphedematous arms (14) with limits of agreement of better than $\pm 6.5\%$ (22). The present results extend this investigation to include the hand and biceps as well as the forearm using a fixed measurement depth associated with the compact TDC device. Similar to these previous findings for forearm TDC measurements the new results indicate that a single TDC measurement may be sufficient at forearm and also at the biceps provided that an approximately 5% differential is acceptable. The LOA analyses more precisely show the extent of agreement but the decision as to whether one accepts the methods as being suitable to be used interchangeably in a clinical setting requires a judgment based on whether the LOA is sufficiently small for the clinical purpose of the measurement. Here interchangeability means that either method could reliably be used to measure a patient. The present results indicate that for the forearm and biceps the LOA values of less than $\pm 5\%$ likely qualifies but that at the hand with an LOA of $+11.1\%$ to -13.3% at least triplicate measurements should be used.

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