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Age-related changes in male forearm skin-to-fat tissue dielectric constant at 300 MHz

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Summary

Prior research suggests that tissue dielectric constant (TDC) values are useful to assess localized skin water in females for early diagnosing breast cancer treatment-related lymphoedema and TDC values in young adults have shown gender differences. However, no TDC data are available for older males nor have ageing effects been studied despite known shifts in water state and other skin age-related changes. Thus our goals were to (i) characterize TDC values at various skin depths in young and older males, (ii) determine the dependence of these values on body composition parameters and (iii) establish inter-arm TDC ratios for use as normal male reference values. TDC measurements were made to depths of 0·5, 1·5, 2·5 and 5·0 mm bilaterally on volar forearm skin in 60 males in three groups of 20 that had mean ages ± SD of 24·0 ± 0·9, 40·0 ± 12·9 and 71·0 ± 8·0 years. Total body fat and water percentages were determined via bioimpedance at 50 KHz. Results showed that (i) for all age groups TDC values decreased with increasing depth, (ii) TDC values were not statistically different among age groups except at a depth of 0·5 mm, (iii) TDC values were highly negatively correlated with total body fat and (iv) inter-arm ratios varied little among age groups and depths. It is concluded that (i) age-related larger TDC values at only the shallowest depth is consistent with skin water shifting state from bound to more mobile in the oldest group and (ii) inter-arm ratios at any depth provide a basis to test for unilateral oedema.

Introduction

Prior research (Mayrovitz *et al.*, 2010) used measurements of skin tissue dielectric constant (TDC) at 300 MHz to characterize and compare young adult male and female skin properties to a skin depth of 1·5 mm. The results demonstrated a 13% greater TDC value in males and concluded that such measurements are useful but when used in research or clinical evaluations must consider this difference in experimental design and data interpretation. This is important as skin TDC values largely depend on water content and are used to characterize the presence and extent of oedema or lymphoedema (Mayrovitz *et al.*, 2014, 2015). However, it is unknown if values obtained in this young adult population carry over into older ages. This is especially relevant to TDC data for males as most prior data are based on female evaluations. There are several reasons why it is important to consider possible male age-related TDC differences and why such differences are expected.

From the point of view of clinical need, we may reference lymphoedema secondary to cancer treatment in males. Ageing brings on an increased likelihood of prostate and breast cancer (Fentiman *et al.*, 2006; Ottini *et al.*, 2010; Bermejo *et al.*, 2015). Conditions that treatments for both conditions can include surgery and radiation (Lyman *et al.*, 2005; Fentiman *et al.*, 2006) and can lead to treatment-related lymphoedema (Oremus *et al.*, 2012; Hsiao *et al.*, 2015). Causes of upper extremity oedema and lymphoedema in addition to breast cancer include melanoma surgery and axillary venous thrombosis. Male breast cancer incidence has a worldwide high incident rate of 12·4 cases per million man-years and a low incident rate of 1·6 per million man-years (Ly *et al.*, 2013). The incidence rate in Scandinavian countries is about four cases per million man-years (Miao *et al.*, 2011). Although male breast cancer is rare, it is reported on the rise (Ottini *et al.*, 2010). Further, whereas female breast cancer has a bimodal incidence peaking at ages of 52 and 71, male breast cancer has a uni-modal age of onset at about 70 years and has a more severe cancer staging at the time of diagnosis with >40% of cases staging at either a tumour grade III/IV (Fentiman *et al.*, 2006a, 2006b; Johansen Taber *et al.*, 2010). Such high cancer stages at diagnosis often require more aggressive treatment regimens, thereby increasing the likelihood of post-treatment lymphoedema. Since, undiagnosed lymphoedema worsens with time, the earlier that it is detected and treated the better the outcome (Ostby *et al.*, 2014). Prior work targeted early detection using TDC measurements only on female breast cancer related lymphoedema (Mayrovitz et al., 2015) as TDC values are directly related to skin water content (Mayrovitz et al., 2013a,b), thereby registering changes in tissue water.

From the point of view of expectations of age-related differences in skin TDC values, we note that ageing is associated with intrinsic and ultraviolet-induced skin changes that alter skin structural (Gniadecka & Jemec, 1998; Diridollou et al., 2001; Gambichler et al., 2006), mechanical properties (Luebberding et al., 2014) and water content and state (Gniadecka et al., 1998a,b; Boireau-Adamezyk et al., 2014a,b) thereby likely affecting TDC values. Examples of likely age-related skin changes relevant to its impact on TDC values include a shift in water state from being mainly bound to proteins and other macromolecules (bound water) to becoming more mobile or free water with increasing skin age. Indeed, it has been reported that skin water is largely present as bound water (Gniadecka et al., 1998a,b) either tightly or loosely bound to macromolecules (Xiao et al., 2012; Boireau-Adamezyk et al., 2014a,b) but shift towards increased percentages of more mobile water with skin ageing (Gniadecka & Jemec, 1998; Gniadecka et al., 1998a; Gniadecka et al., 1998b). As bound water (Pethig, 1992) has a lower dielectric constant than mobile water (Schwan, 1965; Grant, 1966; Pennock & Schwan, 1969), such a shift if present would be associated with increased TDC values. A shift to a greater proportion of non-hydrogen bound water in photo aged skin has been reported to be about 30% greater in dorsal forearm skin (Gniadecka et al., 1998a) with an associated age-related thinning of dorsal and ventral forearm skin (Gniadecka & Jemec, 1998). Magnetic resonance imaging of forearm skin has also demonstrated an increase in dermal mobile water with age (Richard et al., 1993; Querleux, 2004) although some other data suggest only a small age-related difference (Boireau-Adamezyk et al., 2014a,b).

We thus hypothesized that a further manifestation of such changes in water state should cause an age-dependent increase in skin TDC that would be detectible at various depths below the skin surface within and below the dermis. Thus, one aim of our study was to test this hypothesis by measuring skin TDC values to multiple skin depths in younger and older males.

A second aim was to provide initial reference TDC ranges suitable for use with young and especially for older men as no such data are available for older age males. This aim derives from the fact that skin-to-fat TDC values have shown promise as a way to characterize localized skin water changes in many clinically related circumstances. These include water changes associated with weight loss (Laaksonen et al., 2003), assessment of oedema associated with various types of skin irritation (Nuutinen et al., 1998; Lahtinen et al., 1999; Miettinen et al., 2006), diabetic skin changes (Mayrovitz et al., 2013a,b) and changes associated with the menstrual cycle (Mayrovitz et al., 2007). TDC values are also used to assess lymphoedema (Mayrovitz, 2007; Mayrovitz et al., 2015). But most of this information is known only for females whereas data on older age males is rare.

Methods

Subjects

Male volunteers (N = 60) were divided into three age groups (young, older, and oldest) of 20 subjects each with the rationale for age groupings to have three non-overlapping age groups. Group age ranges were for young, 22–25; for older, 26–56; and for oldest, 62–92 years, with corresponding group mean ages (mean ± SD) of 24·0 ± 0·9, 40·0 ± 12·9 and 71·0 ± 8·0, respectively. It may be noted that because of our grouping rationale a greater variation in ages within the 'older' group was present. Subjects were evaluated after the research nature of the study was explained to them, and they had signed an informed consent that was previously approved by the University Institutional Review Board. Exclusionary criteria for participation were if subjects had any known skin condition affecting forearm skin, any injury or open wound on either arm or any prior arm trauma that might have affected tissue water or had previously been treated for breast cancer or had lymph node resection for any purpose or had a cardiac pacemaker. No subjects who volunteered were excluded.

Tissue Dielectric Constant (TDC) measurement method

The dielectric constant or relative permittivity is a dimensionless number equal to the ratio of tissue permittivity to vacuum permittivity. Because TDC values mainly depend on tissue water content, TDC values and their change may provide indices of water content and quantitative estimates of water content changes. For reference, the dielectric constant of distilled water at 32°C is approximately 76. As the device used measures TDC at a frequency of 300 MHz, the values are sensitive to both free and bound water (Pennock & Schwan, 1969). Measuring of the bound water component is important as up to 80–90% of young adult skin water content is bound (Gniadecka et al., 1998a) although this percentage may decrease substantially with ageing (Gniadecka et al., 1998b).

In use the device generates and transmits a very low power 300 MHz signal into a coaxial probe in contact with the skin that acts as an open-ended coaxial transmission line (Stuchly et al., 1981). Part of the signal is absorbed, mainly by tissue water, and part is reflected back to a control unit where the complex reflection coefficient is calculated (Aimoto & Matsumoto, 1996; Lahtinen et al., 1997) from which the dielectric constant is determined (Alanen et al., 1998a,b). Reflections depend on the complex permittivity of the tissue which depend on signal frequency and the dielectric constant (the real part of the complex permittivity) and the conductivity of the tissue with which the probe is in contact. At 300 MHz, the contribution of conductivity to the overall value of the permittivity is small and the TDC is mainly determined by water molecules (free and bound). Further details including validation and repeatability data are described in the literature (Nuutinen *et al.*, 2004; Jensen *et al.*, 2012; Mayrovitz, 2015). Each probe is calibrated against various ethanol–water mixture concentrations each of known dielectric constant values (Mayrovitz, 2015).

Measurement procedure

Tissue dielectric constant measurements were made with the MoistureMeterD (MMD; Delfin Technologies, Kuoppio, Finland). This device measures skin and the skin-to-fat TDC by touching skin with a small hand-held probe for about 10 s. In practice, one of four different probes can be used having outer diameters from 10 mm for a 0·5 mm effective measurement depth to 55 mm for a 5 mm measurement depth. Effective measurement depth is defined as the depth at which the 300 MHz electric field decreases to 1/e of its surface field. In this study, all probes were used allowing for TDC measurements to effective depths of 0·5, 1·5, 2·5 and 5·0 mm. Measurements were taken with subjects seated with arms resting palms up on a lap pillow after they had been resting for at least 5 min. Measurement sites were both volar forearms 6 cm distal to the antecubital fossa with each site measured in triplicate. Probe placement was such to avoid any visible surface veins in areas virtually free of heavy hair growth. Measurements between right and left arm were alternated until three values per arm were obtained. The average of the three measurements was used to characterize the TDC value of each arm. This procedure was performed for each of the four effective measurement depths for the dominant and non-dominant arms. After all TDC measurements were completed, the girth of the forearms at the previously measured TDC sites was measured using a tape measure with a calibrated tension gauge. Biceps girth was also measured in the same way at a position 8 cm proximal to the antecubital fossa. The subjects were then asked to remove their shoes and socks and to stand on a scale for the purpose of measuring their weight and various body composition parameters via bioimpedance measurements at a frequency of 50 KHz (InnerScan Body Composition Monitor, Tanita BC558, Tanita Corporation of America, Inc., IL, USA). The subject stood barefoot on the scale for about 15 s during which time they gripped an electrode in each hand. Parameters measured included percentages of total body water and fat and also limb segmental fat percentages and muscle mass. Total and segmental percentages were determined using specific algorithms within the device based on the whole body and segmental bioimpedance values.

Analysis

All statistical tests were carried out with SPSS (V 13) (IBM North America, NY, USA). TDC values were tested for normality using arm average TDC values that were calculated as the average of the dominant arm (TDCdom) and the non-dominant arm (TDCndom) as it was determined that there was no significant difference in TDC value between sides. Differences in arm average TDC values among age groups were tested using analysis of variance (ANOVA) with *post hoc* comparisons between age groups performed with Bonferroni adjustments such that a P-value of $<0{\cdot}01$ was deemed adequate to deem differences between specific age groups as statistically significant. Comparisons between arms were based on the ratio TDCdom/TDCndom. Differences of arm girths and body composition parameters among age groups were similarly tested by ANOVA. Differences among depths for each age group were tested with ANOVA for each age group separately.

Results

Body composition parameters

Table 1 summarizes the main body composition parameters for each age group. Except for total weight and body mass index values, the oldest group was significantly different in comparison to the young or young and older groups with the oldest group have less total body water percentage, arm girths, and muscle mass and greater whole body and arm fat percentages.

TDC absolute values

Figure 1 summarizes the age and depth dependence of measured TDC values for each of the age groups. For each age group, TDC arm average values decreased with increasing effective measurement depth ($P < 0{\cdot}001$). With respect to age-related differences, only TDC values measured to a depth of 0·5 mm proved to be significantly age dependent with a significantly greater value for the oldest age group ($P < 0{\cdot}01$).

TDC ratios

In contrast to the depth dependence of TDC values, inter-arm ratios (dominant/non-dominant) were not significantly dependent on depth or age with all ratio values summarized in Table 2 with no significant difference in ratios among age groups for any depth or any significant difference in ratios among depths for each age group. By including the data for all 60 subjects, an overall inter-arm ratio based on 60 subjects could be determined with values shown in Table 1. From these data, a conservative threshold ratio for detecting the presence of unilateral oedema or lymphoedema can be calculated by adding to the overall mean ratio a value of 2·5 SD. Threshold ratios calculated in this way range from 1·18 to 1·25 as shown in Table 1.

Correlations among parameters

Within each age group, there was a significant negative correlation between TDC values with total and arm fat percentages

Table 1 Body composition parameters.

	Young group (N = 20)	Older group (N = 20)	Oldest group (N = 20)	Overall P-value
Age (years)	24·0 ± 0·9	40·0 ± 12·8	71·0 ± 8·0[a]	<0·001
Weight (Kg)	81·8 ± 11·2	89·9 ± 17·6	80·6 ± 11·1	0·072
BMI (Kg/m^2)	25·2 ± 3·2	28·0 ± 5·0	26·8 ± 3·9	0·098
Body water (%)	59·1 ± 5·0	55·4 ± 6·3	53·7 ± 5·3[a]	<0·010
Body fat (%)	16·5 ± 6·2	22·0 ± 8·5	25·0 ± 7·3[a]	<0·010
Arm fat (%)	17·0 ± 5·8	21·2 ± 7·0	23·2 ± 6·3[a]	<0·010
Muscle mass arms (Lbs)	8·1 ± 1·0	8·3 ± 1·3	6·7 ± 1·2[b]	<0·001
Muscle mass total (Lbs)	141·4 ± 14·0	144·8 ± 18·0	125·9 ± 14·9[b]	<0·001
Girth forearm (cm)	27·1 ± 1·5	28·3 ± 2·3	26·0 ± 2·2[b]	<0·01
Girth biceps (cm)	29·6 ± 1·6	30·2 ± 2·7	27·5 ± 2·7[b]	<0·01

Overall P-value pertains to significance of difference among all three age groups.
[a]Significantly different from young group, $P < 0·01$.
[b]Oldest group significantly different from young and older groups, $P < 0·01$.

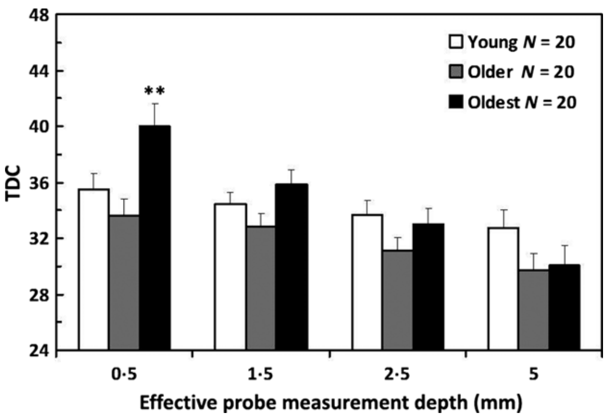

Figure 1 TDC values by depth and age group. For each age group, TDC values monotonically decrease with increasing depth with all depths significantly different than all others ($P < 0·001$). There is a significant difference among age groups only for the oldest group at a depth of 0·5 mm, **$P < 0·01$.

with correlations that became stronger with increasing effective measurement depth as shown in Table 3 for total body fat percentages. There were also corresponding positive correlations between TDC values and total body percentage water. For the three age groups at a measurement depth of 5·0 mm, these ranged from 0·672 to 0·735 ($P < 0·001$).

Discussion

Investigations of potential age-related differences in skin properties have previously focused on a variety of skin features including skin thickness (Gniadecka & Jemec, 1998; Diridollou *et al.*, 2001; Querleux *et al.*, 2009), transepidermal water loss (Chilcott & Farrar, 2000; Machado *et al.*, 2010; Luebberding *et al.*, 2013a,b), mechanical properties (Escoffier *et al.*, 1989; Pierard *et al.*, 1998; Alexander & Cook, 2006; Boyer *et al.*, 2009, 2012; Krueger *et al.*, 2011; Kim *et al.*, 2013; Luebberding *et al.*, 2014), pH and sebum content (Waller & Maibach, 2005; Man *et al.*, 2009; Schreml *et al.*, 2012) and stratum corneum properties and water content (Diridollou *et al.*, 2007; Egawa & Tagami, 2008; Man *et al.*, 2009; Liu *et al.*, 2012; Boireau-Adamezyk *et al.*, 2014a,b; Sato *et al.*, 2014). To our knowledge, the present is the first systematic investigation and report of age-related differences in skin-to-fat tissue dielectric constant values between young and older males.

TDC dependence on measurement depth

For each age group, absolute TDC values showed a significant decrease as the depth of the skin being measured increased. This is an expected result considering what is known about skin composition. Glycosaminoglycans (GAGs) are normally found in the greatest number just beneath the epidermis with their concentration decreasing with increasing skin depth. These proteins are able to bind up to 1000 times their volume in water (Waller & Maibach, 2006). In addition to bound water, epidermal skin has at least twice the amount of mobile water as dermal skin (Richard *et al.*, 1993). As TDC measurements are based on percentage of free and bound water in the depth being measured, a decreasing TDC value would be expected as with increasing depth there is a lessening percentage of measured water. In addition, with increasing depths more subcutaneous fat contributes to the measurement and as fat has low water content and a low dielectric constant the effective TDC is reduced with increasing depth in the forearm.

TDC age-related dependence

A major new finding based on these TDC measurements of volar forearm skin is that significant age-related differences in TDC magnitude occur only in the oldest group and for that group only within the shallowest skin depth of 0·5 mm (Fig. 1). This effective measurement depth includes the stratum corneum, epidermis and the upper dermis that are regions in which age-related shifts in water state from mostly bound to increasing amounts of free water content has been

Table 2 Inter-arm dominant to non-dominant TDC ratios.

TDC depth (mm)	Ratios (TDCdom/TDCndom) Younger group (*N* = 20)	Older group (*N* = 20)	Oldest group (*N* = 20)	Combined group (*N* = 60)	2·5 SD threshold
0·5	0·985 ± 0·073	1·010 ± 0·082	1·005 ± 0·075	1·000 ± 0·076	1·19
1·5	0·992 ± 0·058	1·017 ± 0·076	1·010 ± 0·070	1·006 ± 0·068	1·18
2·5	0·989 ± 0·072	1·028 ± 0·105	0·996 ± 0·079	0·988 ± 0·093	1·22
5·0	0·948 ± 0·098	1·023 ± 0·125	0·985 ± 0·105	0·985 ± 0·105	1·25

Values are ratios of TDC values (mean ± SD) of dominant to non-dominant forearms at the indicated measurement depths. There was no significant difference in ratios among age groups for any depth or any significant difference in ratios among depths for each age group. The 2·5 SD threshold represents the theoretical inter-arm ratio that if exceeded would indicate oedema or lymphoedema for 99·5% of cases.

Table 3 Correlation coefficients between TDC values and total body fat percentages.

TDC depth (mm)	Younger group (*N* = 20)	Older group (*N* = 20)	Oldest group (*N* = 20)
0·5	−0·438 (0·05)	−0·366 (0·11)	−0·564 (0·010)
1·5	−0·450 (0·04)	−0·481 (0·03)	−0·545 (0·013)
2·5	−0·647 (0·002)	−0·519 (0·019)	−0·643 (0·002)
5·0	−0·745 (0·001)	−0·639 (0·002)	−0·720 (0·001)

Values are Pearson correlation coefficients (r) and associated (*P*-value) of the correlation. Statistical significance of correlation tends to increase with increasing measurement depth.

reported (Gniadecka *et al.*, 1998a,b). This shift is in part related to the fact that in young skin water exists primarily in a bound state attached to proteins but as skin ages this changes to a free water state in which water binds to itself in a tetrahedron conformation due to altered protein folding. Thus, the present finding of a greater TDC value in the oldest age group is consistent with such a water state shift as mobile water has a greater dielectric constant than does bound water (Schwan, 1965; Grant, 1966; Pennock & Schwan, 1969).

The fact that a greater TDC value is evident only to a depth of 0·5 mm and not at greater depths may be due to the inclusion of increasing amounts of low water content fat in the measured volume. As noted above, TDC measurements to a depth of 0·5 mm would include all of the epidermis and a portion of the dermis, but measurements to a depth of 1·5 mm and below include the dermis and also include increasing percentages of hypodermis with its low water content fat. Thus, the expected increase in TDC values due to a shift in epidermal and dermal water to a more mobile state might be blunted by including greater amounts of fat-rich hypodermis. This process could explain the non-significant difference in TDC values between age groups at all measurement depths of 1·5 mm and greater. It is unlikely that reported ventral forearm dermis thickness reductions (Gniadecka & Jemec, 1998) would be majorly involved as a preferentially greater reduction of the oldest skin thickness would tend to reduce not elevate the TDC measurement at all depths. Another possibility to consider for the apparent selective age-related increase in TDC only in the oldest population at the shallowest depth is a loss of lamellar bodies as a person ages. An associated decrease in total lipid content might increase the TDC due to increased water to lipid ratio only at this most shallow depth (Ghadially *et al.*, 1995). It is also possible that photo-ageing effects, which hasten the transition from mobile to free water, were most dominant in the oldest subjects selectively affecting the shallower skin depths. Although the volar forearm is not as fully exposed to sun damage as the forearm dorsum, it is not as protected to ultraviolet-related changes over a lifetime as for example buttock skin. It is possible that it is not until the oldest ages measured that this site sustains enough UV-induced damage to have a significant increase in water content.

TDC dependence on body composition parameters

As the older group had significantly more whole body and arm fat and less body water and muscle mass than young (Table 1), one would possibly expect reduced TDC in the older group. That this was not the case indicates that although body composition parameters affect TDC values they do not seem to importantly influence age-related differences.

However, a new finding was the fact that TDC values were highly correlated with body composition parameters and that the magnitude of these correlations increased with increasing measurement depth (Table 3). The significant negative correlation between TDC values and total body fat percentage would be consistent with the increased contribution of low-water containing fat with increasing percentages of the total measurement volume as measurement depth increased. This result indicates that assessments of absolute TDC values for the purposes of assessing skin features in various or different populations should additionally consider body composition parameters as possible confounding factors.

TDC inter-arm ratio reference values

The final new outcome of the present work is the evolution of reference values for inter-arm TDC ratios for males of various ages (Table 2). Such reference values have been reported for females (Mayrovitz *et al.*, 2014) and have been used to assess the presence of breast cancer treatment-related lymphoedema with threshold values ranging from about 1·2–1·3 (Mayrovitz *et al.*, 2015). In the present study of males, absolute TDC values differed by depth, but the inter-arm ratios did not much vary by either depth or age group. Based on these results, we would suggest a threshold based on 2·5 SD with an inter-arm TDC ratio exceeding 1·25 to be taken as strong likelihood of the presence of sub-clinical oedema or lymphoedema. However, this is based on variations from the normal population and would need to be subsequently verified. Further, the selection of 2·5 SD is arbitrary and chosen to statistically include 99·5% of cases. Other levels such as 2 SD to include 97·7% of cases SD to include 99·9% of cases may be indicated in a given situation.

Conflict of interest

The authors have no conflict of interests.

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