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Can tissue dielectric constant measurement aid in differentiating lymphoedema from lipoedema in women with swollen legs?*

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Summary

Background Distinguishing lymphoedema from lipoedema in women with swollen legs can be difficult. Local tissue water content can be quantified using tissue dielectric constant (TDC) measurements.

Objectives To examine whether TDC measurements can differentiate untreated lower extremity lymphoedema from lipoedema, and to test interobserver agreement.

Methods Thirty-nine women participated in the study; 10 patients with lipoedema (LipP), nine patients with untreated lymphoedema (U-LP), 10 patients with lymphoedema treated with compression bandaging for ≥ 4 weeks (T-LP) and 10 healthy controls. All subjects were measured at three predefined sites (foot, ankle and lower leg). All groups except U-LP were measured by three blinded investigators. Using a handheld device, a 300-MHz electromagnetic wave is transmitted into the skin via a 2·5-mm depth probe. TDC calculated from the reflected wave is directly proportional to tissue water content ranging from 1 (vacuum) to 78·5 (pure water).

Results Mean ± SD TDC values for U-LP were 48·8 ± 5·2. TDC values of T-LP, LipP and controls were 34·0 ± 6·6, 29·5 ± 6·2 and 32·3 ± 5·7, respectively. U-LP had significantly higher TDC values in all measurement sites compared with all other groups ($P < 0·001$). A cut-off value of 40 for ankle and lower-leg measurements correctly differentiated all U-LP from LipP and controls. Intraclass correlation coefficients were 0·94 for the ankle and the lower leg and 0·63 for the foot.

Conclusions TDC values of U-LP were significantly higher than those of T-LP, LipP and controls and may aid in differentiating lymphoedema from lipoedema. Interobserver agreement was high in ankle and lower-leg measurements but low in foot measurements.

What's already known about this topic?

- Distinguishing lipoedema from lymphoedema in women with swollen legs can be difficult and time consuming.
- Local tissue water content can be quantified using tissue dielectric constant (TDC) measurements.

What does this study add?

- TDC values were significantly higher in patients with untreated lymphoedema than in all patients with lipoedema, healthy controls and patients with lymphoedema treated with compression for ≥ 4 weeks.
- Interobserver agreement was high in ankle and lower-leg measurements but low in foot measurements.

Lymphoedema is characterized by chronic regional swelling due to accumulation of interstitial fluid in the skin and subcutis caused by a deficiency in the lymphatic system.[1,2] In the later stages tissue remodelling causes skin thickening, fibrosis and subcutaneous adipose tissue deposition.[3] Lipoedema, which affects women almost exclusively, is characterized by bilateral, symmetrical enlargement of the lower extremities owing to abnormal deposits of subcutaneous fat, typically from the buttocks to the ankles, with sparing of the feet.[4] It has been reported that 10–20% of patients referred to lymphoedema clinics are subsequently diagnosed with lipoedema.[5,6] Lipoedema and lymphoedema can be differentiated on medical history and clinical findings. However, it is often difficult to distinguish the two conditions, even for skilled practitioners, and lipoedema is frequently misdiagnosed as lymphoedema.[5] A correct diagnosis is important to ensure optimal treatment. The current gold standard of diagnosing lymphoedema is lymphoscintigraphy, which is a costly and time-consuming examination.

Measurement of the tissue dielectric constant (TDC) is a technique that quantitatively measures local total (intra- and extracellular) tissue water content in human skin and subcutis.[7] The technique has been validated experimentally on skin phantoms.[7–10] Clinical studies on healthy subjects have demonstrated good intra- and interobserver agreement.[11,12] It has been demonstrated that TDC values are influenced by anatomical measurement site,[12,13] measurement depth,[13,14] and subject sex,[15] body mass index (BMI) and age.[14] TDC measurements have been applied successfully in clinical studies evaluating oedema of varying aetiologies, and oedema changes in skin irritation,[16] skin irradiation,[17,18] haemodialysis,[19] postcardiac surgery,[20] breast-cancer-related arm lymphoedema[11,21,22] and lymphoedema of the lower extremities.[23,24]

The primary purpose of our study was to determine whether local tissue water quantification using TDC measurements can effectively differentiate lymphoedema from lipoedema in women with chronic swelling of the lower extremities. A secondary aim was to test interobserver agreement.

Patients and methods

Subject selection

Initially 30 subjects were included in the study: 10 healthy controls, 10 patients with confirmed diagnosis of lipoedema and 10 patients with confirmed diagnosis of lymphoedema. Patients were recruited from the Lymphoedema Center outpatient clinic at the Copenhagen Wound Healing Center, Bispebjerg University Hospital, Copenhagen.[6,25] Only women were included, as lipoedema affects women almost exclusively.

Inclusion criteria for patients with lymphoedema were clinically moderate-to-severe swelling of one or both lower extremities, a normal venous duplex scan and a diagnosis of lymphoedema obtained by medical history and clinical findings, and confirmed by lymphoscintigraphy. As the study was not performed until results from these investigations were known, all 10 patients with lymphoedema had received compression treatment for at least 4 weeks prior to the study day. Treatment consisted of inelastic multicomponent bandaging followed by a maintenance phase using made-to-measure compression stockings, compression class II–III. All patients with treated lymphoedema (T-LP) were wearing compression stockings at the day of measurement and presented only minor or no visible oedema.

Therefore a second part of the study included a group of nine consecutive newly referred patients with untreated lymphoedema (U-LP; no treatment for at least 4 weeks). TDC measurements were performed at the initial visit to the clinic if the patient medical history and clinical findings suggested a diagnosis of lymphoedema. Patients were later excluded if the venous duplex scan was abnormal, or if lymphoscintigraphy did not confirm the diagnosis.

The inclusion criteria for patients with lipoedema (LipP) were normal lymphoscintigraphy and venous duplex scan, dual energy X-ray absorptiometry showing asymmetrical fat distribution between the upper and lower body, and at least four of the following six criteria: (i) bilateral and symmetrical swelling of the lower extremities, (ii) family history of lipoedema, (iii) onset during teenage years or pregnancy, (iv) minimal involvement of the feet, (v) pain, tenderness and easy bruising, and (vi) persistent enlargement of the lower extremities after weight loss.[4,26]

Inclusion criteria for the healthy controls were no known disease, a medical history with no symptoms of leg swelling and normal clinical findings.

The general exclusion criteria were clinical signs of venous insufficiency, history of renal, hepatic or cardiac failure, current treatment with any kind of medication known to affect normal fluid balance, and inflammation of the skin in the measurement areas.

Procedure

T-LP, LipP and controls were all measured over a period of 3 days in a standardized, single-blinded set-up. Firstly, subjects rested in a chair with both feet placed on the floor for 20 min. Then clothes and any compression garments were removed and blinding was performed. The blinding of the three investigators to subject identity and diagnosis was performed by S.B. in the following way. The subject was placed on a chair behind a screen and was asked to place the swollen leg on a knee-high bed rest through a small opening in the screen. Subjects with swelling of both lower legs were asked to present the leg with most symptoms. The size of the lower leg presented was concealed under a wrapping. Three areas of skin marked with a circle of approximately 4 cm in diameter were visible through holes in the wrapping at standardized anatomical measurement sites: the dorsum of the central part of the middle foot, posterior to the medial malleolus, and the lateral part of the lower leg halfway between the knee joint and the lateral malleolus (Fig. 1). The time from removal of

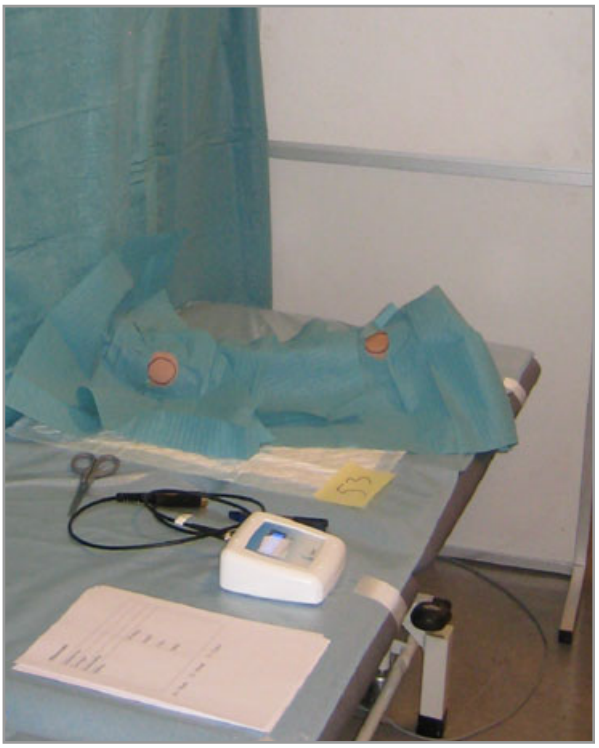

Fig 1. Demonstration of the standardized, single-blinded set-up. The subject is seated behind the screen (left side), presenting only one lower leg. The size of the leg is concealed by a wrapping leaving three circular areas of skin visible to the investigator.

clothes and any compression garments to first measurement was approximately 5 min.

The sequence of the three independent investigators (T.K., S.N. and M.R.J.) was randomized by dice throws for each of the 30 subjects. In one sequence each investigator performed a single TDC measurement in the centre of the marked skin area at each of the three measurement sites. All measurements were completed within a 5-min period for each subject. Results were noted on anonymized forms and stored in a sealed letterbox-type container.

The nine consecutive newly referred U-LP were measured following exactly the same protocol, including the resting period of 20 min. However, for practical reasons they were measured by only one unblinded investigator (T.K.) at the three standardized anatomical measurement sites at the initial visit to the clinic. Disclosure of any results did not take place until the last subject had been examined.

Tissue dielectric constant measurement

Local TDC was measured using the MoistureMeter D® (Delfin Technologies Ltd, Kuopio, Finland). A handheld electronic control unit transmits a 300-MHz electromagnetic wave into a coaxial line and further into an open-ended coaxial probe placed in contact with the skin. The electromagnetic wave is partially absorbed in the tissue and the remainder is reflected/scattered. At 300 MHz the main absorption of energy occurs primarily in tissue water molecules.[27,28] From the reflected wave an electrical parameter directly proportional to local tissue water content, called the TDC, is calculated by the control unit.[19] TDC is a unitless physical quantity ranging from 1 in vacuum to 78·5 in pure water.[29] The diameter of the probe defines the measurement area, while the distance between the two concentric electrodes determines measurement depth.[17,30] Four probes are designed to allow measurement at effective depths of 0·5, 1·5, 2·5 and 5·0 mm. The effective depth is the so-called 1/e penetration depth, meaning the depth at which the electric field has attenuated to 37% of its value at the surface.[30]

The applied probe (M25) measures local TDC at an effective depth of 2·5 mm. M25 was chosen, as Mayrovitz.[23] found a significant difference in TCD between patients with lymphoedema and healthy controls using this probe. The probe has an outside diameter of 23 mm, with a 5-mm spacing between the inner and outer concentric electrodes. The probe was placed manually on the skin surface, ensuring full skin contact with minimal pressure and avoiding any visible veins.

Statistics

Sample-size calculation performed prior to study initiation showed that a minimum of seven subjects was required in each group in order to reach statistical significance. Statistical calculations were performed using SPSS 20 (IBM, Armonk, NY, U.S.A.). Patient age, BMI and TDC values were normally distributed. Results are presented as mean ± SD. One-way ANOVA was performed to test for statistical differences in subject age and BMI in the four groups. To compare TDC values with respect to diagnosis and anatomical location, a two-way ANOVA was used with a Holm–Šidák post-test. Interobserver agreement was calculated using the intraclass correlation coefficient (ICC). As all of the initial 30 subjects were measured by the same three investigators, a consistency-type two-way mixed model was adopted, and 95% confidence intervals (CIs) were calculated. A P-value $< 0{\cdot}05$ was accepted as statistically significant.

Ethics

The study was performed in accordance with the Helsinki II Declaration. Oral and written information about the project was given, and signed consent forms were obtained from all subjects prior to participation. The study was approved by the Science Ethics Committee of the Capital Region of Denmark (H-2-2010-069).

Results

In total 39 women, aged 20–73 years, participated in the study. The nine U-LP included in the second part of the study all had a normal venous duplex scan and abnormal lympho-

scintigraphy, and none had to be excluded. No participants except the T-LP were using any kind of compression.

There was no statistical difference in age and BMI between the four groups (Table 1). Mean TDC values in the four groups with respect to anatomical location are shown in Table 2.

The mean TDC values of U-LP were significantly higher at all three anatomical locations compared with all of the other groups ($P < 0{\cdot}001$). The lower-leg measurements of U-LP and LipP demonstrated the greatest difference in mean TDC value (mean difference 25·7). The mean TDC values of T-LP were significantly higher compared with LipP for the ankle and lower-leg measurements ($P = 0{\cdot}041$ and 0·002, respectively), while there were no differences between the T-LP and the controls at any location ($P \geq 0{\cdot}228$). Except for lower-leg measurements ($P = 0{\cdot}049$), there was no significant difference between LipP and controls (Table 3).

No statistical difference was found between ankle and lower-leg TDC values within each group. However, in T-LP, LipP and healthy controls, the foot TDC values were significantly higher than the ankle and lower-leg TDC values. The foot TDC values of U-LP were significantly below the lower-leg values.

TDC measurements performed by one investigator (T.K.) are presented in Figure 2. A cut-off value of 40 for all measurements (at all sites) differentiates U-LP from LipP and controls with a sensitivity of 93% and a specificity of 90%. The positive predictive value is 0·81 and the negative predictive value is 0·96. Taking into account only measurements performed on the ankle and/or the lower leg, the cut-off value of 40 correctly differentiates all U-LP from LipP and healthy controls.

The interobserver agreement (ICC) of TDC measurements performed by the three independent investigators on T-LP, LipP and controls was 0·633 (95% CI 0·433–0·792) for the foot, 0·937 (0·886–0·968) for the ankle and 0·935 (0·882–0·967) for the lower leg. An ICC of 1 indicates complete agreement, ICC > 0·9 is generally accepted as excellent

Table 1 Distribution of age and body mass index (BMI) in the four groups

	U-LP (n = 9)	T-LP (n = 10)	LipP (n = 10)	Controls (n = 10)	P-value
Age (years)	51·7 (14·3)	43·0 (12·4)	40·7 (10·2)	47·6 (10·5)	0·21
BMI (kg m^{-2})	36·4 (11·3)	30·2 (10·5)	28·5 (6·6)	28·7 (4·4)	0·26

Values are mean (SD). U-LP, patients with untreated lymphoedema; T-LP, patients with treated lymphoedema; LipP, patients with lipoedema.

Table 2 Tissue dielectric constant (TDC) values with respect to group and anatomical measurement site

	U-LP (n = 9)	T-LP (n = 10)	LipP (n = 10)	Controls (n = 10)
Foot	46·2 (6·6)	37·5 (6·8)	36·0 (5·6)	37·3 (6·9)
Ankle	48·7 (4·0)	31·6 (4·7)	26·9 (3·6)	29·3 (2·0)
Lower leg	51·4 (3·9)	33·0 (7·2)	25·7 (2·9)	30·2 (3·4)
All locations	48·8 (5·2)	34·0 (6·6)	29·5 (6·2)	32·3 (5·7)

Values are mean (SD). TDC values of patients with treated lymphoedema (T-LP), patients with lipoedema (LipP) and controls are based on the average values obtained from three independent investigators. TDC values of patients with untreated lymphoedema (U-LP) are based on measurements performed by only one investigator.

Table 3 Comparison of tissue dielectric constant (TDC) values according to group and location, P-values

	U-LP vs. T-LP	U-LP vs. LipP	U-LP vs. controls	T-LP vs. LipP	T-LP vs. controls	LipP vs. controls
Foot	< 0·001	< 0·001	< 0·001	0·486 (NS)	0·916 (NS)	0·554 (NS)
Ankle	< 0·001	< 0·001	< 0·001	0·041	0·313 (NS)	0·292 (NS)
Lower leg	< 0·001	< 0·001	< 0·001	0·002	0·228 (NS)	0·049

NS, not significant. The TDC values of untreated patients with lymphoedema (U-LP) were significantly higher at all three measurement sites compared with all of the other groups. The TDC values of treated patients with lymphoedema (T-LP) were significantly higher than those of patients with lipoedema (LipP) in the ankle and lower leg. The TDC values of LipP were significantly lower than controls in lower-leg measurements.

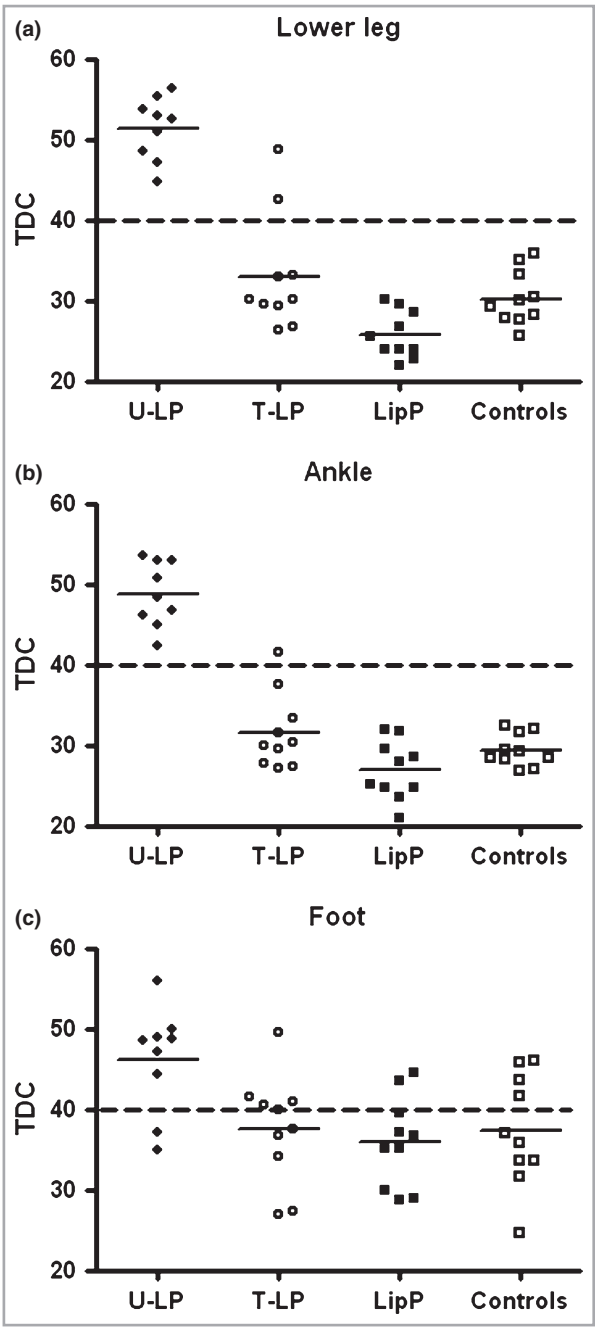

Fig 2. Tissue dielectric constant (TDC) measurements performed by one investigator (T.K.). Single TDC values and mean values are shown for each group at each measurement site. (a) Lower leg, (b) ankle and (c) foot. U-LP, patients with untreated lymphoedema; T-LP, patients with treated lymphoedema; LipP, patients with lipoedema.

agreement and ICC < 0·8 represents questionable agreement.[31] As U-LP were measured by only one investigator the ICC does not apply to this group.

Discussion

In this study we found that the TDC values of U-LP were significantly higher than those of LipP, healthy controls and T-LP. Interobserver agreement was high in ankle and lower-leg measurements but low in foot measurements. To our knowledge this is the first study comparing lymphoedema and lipoedema conditions using this measurement technique.

Our study included a relatively modest number of well-defined patients. Yet for lower-leg and ankle measurements we found a rather large difference in mean TDC value, small SDs, good reproducibility and no overlapping values between U-LP and LipP/controls. With a cut-off value of 40 for ankle and lower-leg measurements, all U-LP were correctly differentiated from LipP and controls. This finding correlates well with an earlier study performed by our group[12] showing that 95% (mean + 2 SD) of TDC values of 34 healthy women were < 38·3 for lower-leg measurements and < 35·2 for ankle measurements. However, whether TDC measurements can be used as an effective tool to differentiate lymphoedema from lipoedema, or oedema from nonoedema, in the initial evaluation of swollen legs in a clinical setting, and whether a clinically relevant cut-off value can be determined, will depend on a prospective study on a larger population.

Other assessment methods used to determine the quality and quantity of chronic local swelling are magnetic resonance imaging (MRI) and computed tomography (CT) scans, which allow visualization of structural changes attributable to lymphoedema or lipoedema. The honeycomb distribution of oedema within the epifascial plane, along with thickening of the skin, is characteristic of lymphoedema, while increased layers of homogeneous subcutaneous fat have been demonstrated in patients with lipoedema.[32–34] High-frequency (20-MHz) ultrasound can visualize an increase in skin thickness and hypoechogenicity in patients with oedema.[35–38] A previous study has demonstrated that high-frequency ultrasound can be used to separate lymphoedema from lipoedema based on a qualitative evaluation of ultrasound images.[26] Compared with these techniques, TDC measurement has the advantage of being readily available in a clinical setting, of low cost and with no ionizing radiation. Unlike CT and MRI scans, TDC measurements can be performed in highly obese subjects, a common problem in patients with lymphoedema and lipoedema. Operating the device and reading the result requires no expert training. However, interpretation of TDC values when diagnosis is unknown will require training and experience.

The TDC values of the foot were significantly different from the ankle and lower-leg values. Previous studies have demonstrated that TDC values vary between different anatomical regions, as the TDC value is influenced by different layers of tissue at different measurement sites.[8,12,13,39] Subcutis and fat are known to have relatively low water content, while dermis, connective tissue (including tendons), blood vessels, muscle, bone and nerves have a relatively high water content.[40] The thin layer of subcutis found on the dorsum of the foot in subjects without swelling may cause the TDC measurement at the effective depth of 2·5 mm to involve more tissues with high water content, resulting in a higher TDC value. Contrary to what one might expect, the foot TDC values of U-LP were significantly below

the lower-leg values. An explanation could be that chronic changes (fibrosis and fat accumulation seen in long-lasting oedema)[41] might be more advanced in the distal areas; however, further investigations are needed to clarify this finding.

Foot TDC values also demonstrated poor interobserver agreement and larger SDs. The presence of a network of large superficial veins found on the dorsum of the foot could offer an explanation, as even a slight deviation in probe position may result in a fairly large difference in the tissue composition of the measured area.

Although no statistical difference in BMI was found between the four groups, U-LP were on average severely obese, while the other three groups were overweight to moderately obese. If this is caused by excess fat mass, partly accumulated in the subcutis, the difference would cause the TDC values of U-LP to decrease owing to the low water content of fat tissue. However, the tendency could also be explained by the excessive amounts of fluid in the legs of U-LP, causing TDC values to become high.

The TDC values found in T-LP were significantly lower than the values found in U-LP. This finding corresponds well to the clinically decreased oedema volume observed in this group. An earlier study has demonstrated that lymphoedema treatment with manual lymphatic drainage causes a significant reduction in TDC values in lymphoedematous legs,[23] and it is generally accepted that compression treatment can reduce oedema volume in the extremities. The significantly lower TDC values in T-LP are presumably the result of the compression treatment. However, TDC values prior to treatment initiation in T-LP are unknown, and the correlation between compression treatment and the decreased TDC values needs further documentation.

The unblinded measurements of the U-LP in the second part of our study could potentially affect the study results. However, the displayed TDC values were registered as measured, and great care was taken in order to carry out measurements in otherwise exact accordance with the standardized set-up, and at the same standardized anatomical measurement sites.

In conclusion, the TDC values of U-LP were significantly higher than those of T-LP, LipP and controls at all measurement sites. Interobserver agreement was high in ankle and lower-leg measurements but low in foot measurements. Quantification of local tissue water content using TDC measurement might aid the differentiation of untreated lymphoedema from lipoedema in women with chronic swelling of the legs. Potentially, TDC measurement may become a reproducible and cost-effective diagnostic tool in the initial clinical evaluation of swollen legs, aiding correct diagnosis and reducing the need for other costly and cumbersome examinations. However, this will depend on a prospective study on a larger population.

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