Reliability of the MoistureMeterD Compact Device and the Pitting Test to Evaluate Local Tissue Water in Subjects with Breast Cancer-Related Lymphedema

Tessa De Vrieze, PT, MT,[1,2] Nick Gebruers, PhD, PT,[2,3] Ines Nevelsteen, PhD, MD,[4]
An De Groef, PhD, PT, MT,[1] Wiebren A.A. Tjalma, PhD, MD,[3,5,6] Sarah Thomis, MD,[7,8] Lore Dams, PT, MT,[1,2]
Elien Van der Gucht, PT,[1,2] Frauke Penen, PT,[1,2] and Nele Devoogdt, PhD, PT[1,7,8]

Abstract

Background: Local tissue water in patients with breast cancer-related lymphedema (BCRL) can be assessed by measurement of the tissue dielectric constant using the MoistureMeterD Compact® (MMDC) device, or by performing the pitting test. Although these assessment methods are commonly used in clinical practice, literature shows a lack of research on their clinimetric properties. Therefore, the aim of this study was to investigate reliability of both methods, in assessing the upper limb in BCRL.

Methods and Results: Thirty women with BCRL were enrolled. Local tissue water was evaluated at nine reference points on the upper limb and trunk, using both methods. To determine intra- and inter-rater reliability of the MMDC device (using the absolute percentages of water content [PWC%] and interarm PWC% ratios based on single and multiple measures), intraclass correlation coefficients (ICCs), and standard errors of the measurement were calculated. To determine intra- and inter-rater agreement of the pitting test, Cohen's kappa coefficients were calculated as well as percentages of agreement. MMDC measurements yielded moderate to very strong intra- (ICC 0.648–0.947) and inter-rater (ICC 0.606–0.941) reliability, depending on the measurement location on the edematous limb. The pitting test showed a very strong intrarater agreement at nearly all defined points, but a weak inter-rater agreement, especially at the medial elbow and the breast.

Conclusion: This study supports the MMDC device and pitting test as being useful tools in the clinical evaluation of BCRL. However, further research into the concurrent validity of both tools is warranted.

Keywords: breast neoplasms, lymphedema, tissue dielectric constant, pitting test, reliability

Introduction

FOR THE CLINICAL assessment of breast cancer-related lymphedema (BCRL), a variety of whole-arm volume measurement methods is available. The water displacement method and circumference measurements are the most frequently used methods[1] and are recommended as best practice for assessing lymphedema volume in extremities.[2] However, tissue dielectric constant (TDC) measurements are increasingly being applied as a tool to help characterizing edema[3–6] to detect its presence[7,8] and evaluate treatment response.[9–14] This method relies on the measurement of the amount of local tissue water in the skin and has been validated experimentally on skin preparations.[15–18] Sensitivity and

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[1]Department of Rehabilitation Sciences, KU Leuven–University of Leuven, Leuven, Belgium.
[2]Department of Rehabilitation Sciences and Physiotherapy, MOVANT, University of Antwerp, Antwerp, Belgium.
[3]Multidisciplinary Oedema Clinic, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium.
[4]Multidisciplinary Breast Centre, UZ Leuven–University Hospitals Leuven, Leuven, Belgium.
[5]Department of Medicine, MIPRO, University of Antwerp, Antwerp, Belgium.
[6]Multidisciplinary Breast Clinic, Antwerp University Hospital, Antwerp, Belgium.
[7]Department of Vascular Surgery, Centre for Lymphoedema, UZ Leuven–University Hospitals Leuven, Leuven, Belgium.
[8]Department of Physical Medicine and Rehabilitation, Center for Lymphoedema, UZ Leuven–University Hospitals Leuven, Leuven, Belgium.

specificity for TDC measures have shown to be 65.8% and 83.9%, respectively.[19]

The MoistureMeterD Compact® (MMDC) device can be used to determine the TDC in terms of the percentage of water content (PWC%), at any particular site of the body, including the breast, trunk, or other central body parts, in which midline edema can manifest.[20,21] Up to a depth of 2 mm, this portable device allows measuring free and bounded water in the tissue, through which the electromagnetic wave passes.[14] More details about the physics and underlying principles of the device and the dielectric constant in general have been extensively described elsewhere.[7,15,17,22–24]

Despite the widespread use of the MMDC device for diagnosing and evaluating lymphedema, standardized research investigating its clinimetric properties in patients with BCRL is lacking. In a systematic review of Hidding et al.,[2] only one study[25] was listed that investigated interobserver agreement of TDC measurements, showing good reliability for evaluating local tissue water at the ankle (ICC 0.94) and lower leg (ICC 0.94) in patients with lip- or lymphedema. Furthermore, one study investigated intrarater reliability of TDC measures at the self-reported most affected region in edematous upper limbs.[26] Intraclass correlation coefficient (ICC) calculations on interarm TDC ratio results were not performed. Recently, an article was published in which test–retest reliability was investigated for evaluating local tissue water in the upper limb using the MMDC device.[14] However, since this investigation was performed on subjects free of lymphedema, the extent to which these results apply to patients with lymphedema is not known and still needs to be explored. Furthermore, to our knowledge, no study so far has examined reliability of the interarm TDC ratios, in particular, in patients with BCRL. This is surprising as the ratio is the preferred TDC parameter to detect tissue water changes over time in unilateral conditions since studies have shown that absolute TDC values vary by site and depth, but that interarm ratios are relatively independent of it.[6,27]

Next to the MMDC device, a second evaluation technique, the pitting test, can be applied to assess local tissue water in the skin. Pitting is usually tested by firmly pressing on the area of interest for at least 5–10 seconds.[28,29] If an indentation remains when the examiner releases pressure, then pitting is present. The depth of the indentation reflects on the amount of excess interstitial fluid, hence the severity of the edema.[28] Soft tissues affected by lymphedema can change over time, from initially an extracellular fluid-rich edematous stage to a largely fibrotic condition.[26] Consequently, in advanced stages of lymphedema, the subcutaneous tissue can become fibrotic/fatty and will change into a nonpitting edema,[30] which requires an altered approach in the treatment of lymphedema. To our knowledge, no previous studies have investigated reliability of the pitting test, which raises questions to its reproducibility in clinical practice.

Therefore, the aim of current study was to investigate the intra- and interrater reliability of both the MMDC device and the pitting test as easily applicable and noninvasive techniques for evaluating local tissue water in patients with BCRL in clinical practice. Furthermore, and with regard to the reliability of the MMDC device, a comparison was made between the following: (1) results regarding single PWC% measures and the recommended multiple PWC% measures and (2) results regarding absolute PWC% measures and interarm PWC% ratios.

Materials and Methods

Trial design

This cross-sectional study was conducted in accordance with the Declaration of Helsinki and was reported following the recommended STROBE guideline for observational studies. All assessments were performed at the department of Physical Medicine and Rehabilitation of the University Hospitals Leuven. This study is part of the EFforT-BCRL trial,[31] for which approval was obtained by the Ethics Committee of the University Hospitals Leuven (CME reference S58689, EudraCT 2015-004822-33).

Participants

Between July and November 2017, patients of the EFforT-BCRL trial[31] were asked to participate in this subtrial. Eligibility criteria were (1) female/male patients with BCRL of the arm/hand with at least 5% volume difference (corrected for limb dominance) at the time of inclusion in the EFforT-BCRL trial, (2) currently in the maintenance phase of the decongestive lymphatic therapy,[1] and (3) no known recurrence of cancer. Participants were excluded if they had no signs of pitting at any of the measurement points at the time of the testing. All participants received written and oral information by mail as well as by phone. All participants signed the informed consent document before their start in the EFforT-BCRL trial.

Assessment

Descriptive data (participant's age; body mass index; excessive arm volume; lymphedema stage as described by the International Society of Lymphology,[1] location and duration of lymphedema; type of breast surgery and axillary lymph node dissection; side of surgery; hand dominance; type of adjuvant treatment [radiotherapy, chemotherapy, hormonal therapy, or target therapy]) were collected by interviewing the participants and by consulting their medical record.

For each participant, only one visit to the hospital was necessary to collect all data. Participants arrived 15 minutes before the start of the measurements. During this time, compression sleeves and jewelry on both arms were removed.

The estimated duration for a single execution of the MMDC measurements (edematous and nonedematous limb) and the performance of the pitting test (edematous limb), was 30 minutes; that is, one assessment block. Since the execution of an assessment block was performed three times consecutively without breaks in-between (i.e., the first and the last time by assessor 1 [L.V.] and the second time by assessor 2 [T.D.V.]), the total duration of the investigation was ∼1.5 hours per participant. The same sequence of the two measurement methods was maintained among the three assessment blocks for all participants, starting with the MMDC measurements and ending with the pitting test. This order was preferred, since in case pitting is present, the indentation of the skin takes a few minutes to restore. Before the assessments, two different 1-hour training moments were scheduled to guarantee standardization between assessors (T.D.V. and L.V.; Masters in Rehabilitation Sciences and Physiotherapy), who were experts in the field of lymphology, as well as between the persons registering the scores (S.V.D.S.,

A.V.H., M.B., and T.P.; Masters in Rehabilitation Sciences and Physiotherapy). During the training moment for the assessors, agreements were made regarding probe position, patient position, and measurement procedure concerning the TDC measures, as well as regarding pressure time, patient position and measurement procedure concerning the pitting test. During the training moment for the persons registering the scores, the required fill-in documents were discussed in detail to get familiar with the measurement procedures.

TDC measurement procedure. To perform the measurements of local tissue water, this study used a commercially available compact version of an open-ended coaxial probe with medium probe size[20] operating at 300 MHz, called the MMDC device (Delfin Technologies, Kuopio, Finland).[7] The absolute results of the MMDC are based on a ratio scale between 0 and 100, representing the percentage (%) of local tissue water, which is derived from following equation:

Percentage water content (PWC%) = $100 \times$ (measured dielectric constant $-1)/77.5$,[20] and represents an approximate relationship between % local tissue water and TDC.[6] An outcome of 1 would illustrate a vacuum without water, while pure water yields a reading of 78.5.[20]

A total of 18 measurement points were marked with a soft pencil, including 9 reference points on the edematous and 9 on the nonedematous limb and trunk. The location of the measurement points and the positions of the participant were standardized, as shown in Table 1. Each reference point was measured in triplicate, as recommended in the user manual of this device. A single measurement was obtained by placing the probe in contact with the skin, where the pressure sensor inside the device helps to maintain good skin contact. After 3–5 seconds, an audible signal indicated completion of a single measurement. Simultaneously, the displayed PWC% was dictated to a blinded notetaker who wrote down the outcomes on a preset form. The reporting of the local tissue water using the MMDC was performed fourfold: (1) as a single measurement, (2) based on the average of three consecutive measurements (multiple measurements),

(3) based on the calculated interarm PWC% ratios $\left(= \frac{\text{PWC\% value edematous limb}}{\text{PWC\% value non}-\text{edematous limb}} \right)$ for each measurement point using single measurements, and (4) based on the calculated interarm PWC% ratios for each measurement point, using the average of the multiple measurements. Therefore, four datasets were compared: (1) the first out of three PWC% values obtained, (2) the mean of the triplicate PWC% values,[4,32] (3) the calculated interarm ratios based on the first out of three PWC% values obtained, and (4) the calculated interarm ratios based on the mean of the triplicate PWC% values.[4,8,26]

To preserve blinding of the next assessor for the reference points, after completing all the measurements, reference points were completely removed using alcohol wipes. By the time this was finished, all signs of pitting (in case these were present) had been disappeared. Measurements occurred in a room where the average temperature was 22°C.

Pitting measurement procedure. The pitting test involved application of sustained thumb pressure during 5 seconds on the skin and superficial tissue. Each of the nine points on the edematous limb and trunk was examined (Table 1). On release of the applied pressure, an indentation of the tissue at the test site was defined as ''pitting'' and an absence of tissue changes was classified as ''non-pitting.'' After removing the thumb, the tissue was first evaluated visually and subsequently by palpation. Each point was scored on a 3-point ordinal scale, where 0 = no clinical pitting edema, 1 = slight/doubtful pitting and 2 = noticeably pitting. The depth of the indentation and time of tissue rebound were taken into account to provide a score. Similar to the TDC measurement procedure, the test results were dictated to a blinded notetaker.

Data analysis. Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0. The 0.05 level of significance was applied. Descriptive statistics for continuous values are presented as mean ± SD (standard deviation) for normal distributed data and median and

TABLE 1. OVERVIEW OF THE NINE DIFFERENT MEASUREMENT POINTS AND PARTICIPANT'S POSITIONS

Measurement point	Location	Posture
Hand	Central point between dorsal side of the thumb and index	Sitting—Forearm pronation
Ventral side forearm	15 cm distal to the elbow fold	Sitting—Forearm supination
Dorsal side forearm	10 cm distal to caput radii with orientation toward the middle finger	Sitting—Forearm pronation
Medial elbow	3 cm proximal to the medial epicondyle of the humerus	Sitting—Forearm supination
Ventral side upper arm	7 cm proximal to the elbow fold	Sitting—Forearm pronation
Dorsal side upper arm	7 cm proximal to the upper edge of the olecranon	Sitting—Forearm pronation
Lateral shoulder (Deltoid muscle)	5 cm distal to the acromion	Sitting—Forearm pronation
Breast/ventral trunk region	3 cm distal to the nipple or distal to the middle of the scar, if the patient had a mastectomy	Supine lying on table
Lateral trunk	5 cm distal to the dorsal axillary fold	Standing—Dropped arms

Participant position from hand to shoulder: Sitting position—arms in 45° anteflexion, resting on a table.

interquartile range for not normal distributed data. Categorical variables are presented as number and proportion (%).

Intrarater reliability was assessed using $ICC_{3,1}$, two-way mixed model,[33] with 95% confidence intervals (CI) for continuous measures. Inter-rater reliability was assessed with $ICC_{2,1}$, two-way random model.[33] Calculations were based on two examiners assessing each participant and represent the expected reliability of a single examiner rating, as referred to Shrout and Fleiss.[34] ICC values were classified into following categories: values <0.40 represent weak reliability, between 0.40 and 0.74 represent moderate reliability, between 0.75 and 0.90 represent strong reliability, and ≥0.90 represent very strong reliability. For each measurement point, both intra- and inter-rater reliability analyses were conducted for a single measurement, for the average value of the multiple measures, as well as for the interarm PWC ratios based on single and multiple measures.

To interpret the magnitude of the within-subjects variation of the two scores, the standard error of measurement (SEM) was calculated using following formula: $SEM = SD\sqrt{(1 - ICC)}$, where SD was the standard deviation of the outcome differences between the two assessments.[33]

Cohen's kappa and percentage of agreement statistics were calculated to evaluate the intra- and inter-rater reliability of the pitting test on the edematous arm. Kappa values were classified into less than chance agreement ($K < 0.00$), slight agreement ($K = 0.01–0.20$), fair agreement ($K = 0.21–0.40$), moderate agreement ($K = 0.41–0.60$), substantial agreement ($K = 0.61–0.80$), or almost perfect agreement ($K = 0.81–0.99$).[35]

To calculate the percentage of agreement, differences between the two scores on the pitting test were calculated. In case the two scores were the same, this indicated agreement. The total percentage of agreement was calculated for each measurement point as follows: the total number of cases with agreement divided by 30 (No. of participants) and multiplied by 100.

Results

Thirty patients with BCRL were enrolled in this subtrial. The measurements of local tissue water with the MMDC and the pitting test were completed by both raters in all participants.

Participant characteristics

All participants were women (100%). An overview of the characteristics of the included subjects is provided in Table 2.

Intrarater reliability MMDC device

Results regarding intrarater reliability (ICC, SEM) of the MMDC device after a single measurement of % local tissue water, as well as after multiple measures on each of the nine measurement points, are presented in Table 3. Results regarding intrarater reliability (ICC, SEM) of the MMDC device after calculating the interarm PWC% ratio based on a single measurement, as well as based on multiple measures on each measurement point, are shown in Table 4.

TABLE 2. CHARACTERISTICS OF THE INCLUDED SUBJECTS (N = 30)

Variable	Outcome, mean (SD)
Descriptives	
Age, years	65 (8)
Body mass index, kg/m^2	28 (4)
Excessive arm volume, mL	477 (367)
Duration lymphedema, months	74 (44)

	Outcome, n (%)
Frequencies	
Lymphedema stages	
Stage I	3 (10)
Stage IIa	18 (60)
Stage IIb	9 (30)
Location of lymphedema	
Lower arm	14 (53)
Upper arm	0 (0)
Total arm (lower arm+upper arm)	16 (47)
Breast surgery	
Mastectomy	21 (70)
Breast-conserving surgery	9 (30)
Axillary lymph node clearance	
SLNB	0 (0)
ALND	30 (100)
Surgery on the dominant side	17 (57)
Radiotherapy	30 (100)
Chemotherapy	24 (80)
Antihormonal therapy	27 (90)
Target therapy (Herceptin)	6 (20)

ALND. axillary lymph node dissection; SD, standard deviation; SLNB, sentinel lymph node biopsy.

Values of the edematous limb using multiple measures showed strong to very strong ICC values (ICCs ≥0.75) for all measurement points, except for the lateral trunk (ICC 0.710), which showed moderate reliability.

The statistical analysis when using single measurements showed a strong to very strong intrarater reliability (ICC ≥0.75) for all measurement points except for the ventral side of the forearm (ICC 0.664) and for the lateral trunk (ICC 0.648) (moderate reliability).

Values of the nonedematous limb using multiple measures showed, strong to very strong ICC values (ICCs ≥0.75) for all measurement points, except for the lateral trunk (ICC 0.649) (moderate reliability).

The statistical analysis when using single measurements showed a strong to very strong intrarater reliability (ICC ≥0.75) for all measurement points except for the lateral shoulder (ICC 0.699), for the breast (ICC 0.738) and for the lateral trunk (ICC 0.605) (moderate reliability).

Values of the interarm PWC ratios based on multiple measures showed strong intrarater reliability for the measurement points at the hand (ICC 0.852), dorsal side of the forearm (ICC 0.847), ventral side of the upper arm (ICC 0.883), and breast (ICC 0.757).

Analysis of the interarm PWC ratios based on single measurements proved strong to very strong intrarater reliability for the measurement points at the hand (ICC 0.839), ventral side of the upper arm (ICC 0.900), and dorsal side of the upper arm (ICC 0.774).

Table 3. Intra-Rater Reliability MoistureMeterD Compact

	Multiple measurements				Single measurements			
	Rater 1, mean PWC% (SD)	Rater 1, mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)	Rater 1, mean PWC% (SD)	Rater 1, mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)
Edematous limb								
Hand	49.33 (7.35)	48.59 (6.09)	0.917 (0.834–0.960)	1.90 (–2.99 to 4.47)	40.45 (9.73)	49.35 (8.53)	0.909 (0.817–0.956)	2.71 (–4.21 to 6.41)
Ventral side forearm	62.02 (9.04)	61.15 (9.21)	0.793 (0.604–0.897)	4.08 (–7.12 to 8.86)	61.34 (9.72)	60.79 (8.65)	0.664 (0.403–0.826)	5.23 (–9.7 to 10.8)
Dorsal side forearm	55.64 (6.92)	55.35 (6.29)	0.871 (0.750–0.937)	2.33 (–4.27 to 4.87)	55.46 (7.81)	55.32 (5.95)	0.795 (0.612–0.897)	3.06 (–3.86 to 8.14)
Elbow	52.51 (8.22)	52.84 (7.73)	0.889 (0.780–0.945)	2.61 (–4.79 to 5.45)	52.45 (8.27)	52.59 (7.57)	0.797 (0.616–0.898)	3.5 (–6.71 to 6.99)
Ventral side upper arm	44.99 (9.36)	45.86 (8.93)	0.947 (0.891–0.975)	2.07 (–3.16 to 4.96)	44.61 (9.46)	45.61 (8.99)	0.940 (0.875–0.971)	2.12 (–3.35 to 5.35)
Dorsal side upper arm	44.83 (6.60)	44.68 (6.59)	0.790 (0.296–0.922)	3.03 (–5.74 to 6.14)	44.16 (6.49)	44.28 (6.57)	0.888 (0.778–0.945)	2.15 (–4.09 to 4.33)
Lateral shoulder (Deltoid muscle)	46.50 (4.98)	46.45 (4.35)	0.908 (0.816–0.955)	1.39 (–2.68 to 2.78)	46.37 (5.22)	46.64 (4.56)	0.865 (0.719–0.929)	1.77 (–3.29 to 3.63)
Breast/ventral trunk region	51.22 (10.02)	51.77 (10.98)	0.939 (0.876–0.971)	1.76 (0.91–7.81)	51.08 (9.75)	50.90 (9.04)	0.937 (0.871–0.969)	2.32 (–4.36 to 4.72)
Lateral trunk	48.26 (5.28)	46.88 (4.49)	0.710 (0.467–0.852)	3.14 (–2.58 to 9.74)	48.02 (5.24)	46.82 (4.62)	0.648 (0.386–0.814)	2.87 (–4.43 to 6.83)
Nonedematous limb								
Hand	43.76 (5.42)	42.60 (4.41)	0.814 (0.631–0.909)	2.08 (–2.92 to 5.24)	43.73 (5.38)	44.57 (4.36)	0.755 (0.543–0.876)	2.37 (–3.48 to 5.8)
Ventral side forearm	45.63 (7.12)	44.78 (5.94)	0.900 (0.801–0.951)	2.03 (–3.13 to 4.83)	45.13 (7.50)	44.9 (6.02)	0.799 (0.619–0.899)	2.98 (–5.61 to 6.07)
Dorsal side forearm	42.20 (6.86)	41.65 (6.16)	0.945 (0.889–0.974)	1.50 (–2.39 to 3.49)	42.10 (7.10)	41.57 (6.18)	0.943 (0.885–0.973)	1.56 (–2.53 to 3.59)
Elbow	36.76 (5.14)	37.44 (5.32)	0.885 (0.773–0.943)	1.74 (–2.74 to 4.1)	36.69 (4.69)	37.36 (5.40)	0.833 (0.681–0.917)	2.03 (–3.31 to 4.65)
Ventral side upper arm	37.52 (5.37)	36.78 (5.11)	0.882 (0.766–0.942)	1.77 (–2.73 to 4.21)	37.06 (5.49)	36.78 (5.08)	0.861 (0.728–0.931)	1.94 (–3.52 to 4.08)
Dorsal side upper arm	36.51 (4.90)	36.20 (4.76)	0.898 (0.799–0.950)	1.52 (–2.66 to 3.28)	36.63 (4.81)	36.14 (4.89)	0.883 (0.770–0.942)	1.63 (–2.70 to 3.68)
Lateral shoulder (Deltoid muscle)	46.54 (4.84)	45.23 (4.42)	0.859 (0.639–0.939)	1.71 (–2.04 to 4.66)	46.35 (5.06)	44.95 (4.43)	0.699 (0.449–0.846)	2.56 (–3.62 to 6.42)
Breast/ventral trunk region	43.16 (6.49)	45.05 (7.42)	0.777 (0.562–0.890)	3.23 (–4.45 to 8.21)	42.67 (6.53)	44.73 (7.31)	0.738 (0.499–0.870)	3.48 (–4.77 to 8.89)
Lateral trunk	45.60 (4.89)	44.75 (4.58)	0.649 (0.388–0.815)	1.05 (–1.21 to 2.91)	45.06 (4.87)	44.42 (4.76)	0.605 (0.320–0.790)	2.98 (–5.19 to 6.47)

CI, confidence interval; ICC, intraclass correlation coefficient; PWC%, percentage of water content; SEM, standard error of measurement.

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TABLE 4. INTRA-RATER RELIABILITY OF THE INTERARM PERCENTAGE OF WATER CONTENT RATIO

Interarm PWC% ratio

	Multiple measurements				Single measurements			
	Rater 1, interarm PWC% ratio (SD)	Rater 1, interarm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)	Rater 1. interarm PWC% ratio (SD)	Rater 1, interarm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)
Hand	1.14 (0.20)	1.15 (0.14)	0.852 (0.712–0.927)	0.07 (1.03–1.29)	1.17 (0.25)	1.16 (0.19)	0.839 (0.689–0.920)	0.09 (0.98–1.34)
Ventral side forearm	1.35 (0.32)	1.37 (0.14)	0.340 (−0.024 to 0.622)	0.19 (0.48–1.22)	1.39 (0.22)	1.36 (0.15)	0.538 (0.226–0.751)	0.12 (0.61–1.09)
Dorsal side forearm	1.34 (0.19)	1.35 (0.18)	0.847 (0.703–0.924)	0.07 (0.41–0.69)	1.34 (0.21)	1.35 (0.20)	0.740 (0.522–0.867)	0.10 (0.35–0.75)
Medial elbow	1.44 (0.22)	1.42 (0.19)	0.718 (0.488–0.855)	0.11 (0.47–0.89)	1.44 (0.20)	1.42 (0.19)	0.528 (0.210–0.744)	0.17 (0.34–1.02)
Ventral side upper arm	1.20 (0.21)	1.26 (0.23)	0.883 (0.717–0.948)	0.08 (0.59–0.89)	1.21 (0.22)	1.25 (0.21)	0.900 (0.789–0.952)	0.07 (0.61–0.87)
Dorsal side upper arm	0.99 (0.13)	1.24 (0.16)	0.183 (−0.092 to 0.501)	3.01 (−5.58–6.2)	1.21 (0.16)	1.24 (0.16)	0.774 (0.581–0.885)	0.09 (0.14–0.48)
Lateral shoulder (Deltoid muscle)	1.00 (0.08)	1.03 (0.07)	0.723 (0.452–0.865)	0.04 (1.23–1.39)	1.00 (0.09)	1.04 (0.07)	0.446 (0.122–0.688)	0.07 (1.18–1.44)
Breast/ventral trunk region	1.20 (0.22)	1.15 (0.18)	0.757 (0.547–0.877)	0.1 (1.69–2.07)	1.21 (0.22)	1.50 (0.18)	0.734 (0.494–0.866)	0.13 (1.63–2.13)
Lateral trunk	1.06 (0.11)	1.05 (0.09)	0.673 (0.419–0.830)	0.06 (0.74–0.96)	1.07 (0.11)	1.06 (0.1)	0.538 (0.225–0.750)	0.07 (0.7–1)

TABLE 5. INTER-RATER RELIABILITY MOISTUREMETERD COMPACT

	Multiple measurements				Single measurements			
	Rater 1, mean PWC% (SD)	Rater 2, mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)	Rater 1, mean PWC% (SD)	Rater 2, mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)
Edematous limb								
Hand	49.33 (7.35)	48.99 (6.97)	0.881 (0.766–0.941)	2.43 (–4.42 to 5.1)	40.45 (9.73)	50.20 (9.90)	0.858 (0.914–0.980)	3.63 (–7.87 to 7.37)
Ventral side forearm	62.02 (9.04)	60.93 (9.91)	0.606 (0.319–0.792)	5.84 (–10.36 to 12.54)	61.34 (9.72)	60.91 (10.94)	0.897 (0.795–0.950)	3.26 (–5.95 to 6.81)
Dorsal side forearm	55.64 (6.92)	55.19 (6.91)	0.911 (0.823–0.856)	2.03 (–3.52 to 4.44)	55.46 (7.81)	55.06 (7.42)	0.918 (0.836–0.960)	2.14 (–3.8 to 4.6)
Elbow	52.51 (8.22)	50.74 (9.82)	0.784 (0.595–0.891)	4.1 (–6.26 to 9.80)	52.45 (8.27)	50.22 (9.75)	0.636 (0.367–0.807)	5.34 (–8.24 to 12.7)
Ventral side upper arm	44.99 (9.36)	46.95 (9.17)	0.917 (0.775–0.965)	2.62 (–3.18 to 7.1)	44.61 (9.46)	46.72 (9.07)	0.941 (0.973–0.972)	2.21 (–2.23 to 6.45)
Dorsal side upper arm	44.83 (6.60)	48.00 (7.27)	0.790 (0.296–0.922)	3.13 (–2.96 to 9.3)	44.16 (6.49)	47.44 (7.77)	0.711 (0.310–0.873)	3.77 (–4.02 to 10.78)
Lateral shoulder (Deltoid muscle)	46.50 (4.98)	46.82 (5.15)	0.792 (0.609–0.896)	2.27 (–4.15 to 4.77)	46.37 (5.22)	46.68 (5.00)	0.790 (0.603–0.894)	2.31 (–4.21 to 4.83)
Breast/ventral trunk region	51.22 (10.02)	51.78 (10.99)	0.877 (0.759–0.939)	3.62 (–6.54 to 7.66)	51.08 (9.75)	52.00 (11.22)	0.796 (0.616–0.897)	4.65 (–8.2 to 10.04)
Lateral trunk	48.26 (5.28)	48.11 (5.26)	0.726 (0.498–0.860)	2.71 (–5.16 to 5.46)	48.02 (5.24)	48.07 (5.40)	0.643 (0.369–0.813)	3.12 (–6.07 to 6.17)
Nonedematous limb								
Hand	43.76 (5.42)	44.45 (6.16)	0.665 (0.408–0.825)	3.30 (–5.77 to 7.15)	43.73 (5.38)	44.25 (6.15)	0.616 (0.334–0.797)	3.51 (–6.37 to 7.41)
Ventral side forearm	45.63 (7.12)	46.78 (7.36)	0.895 (0.785–0.950)	2.31 (–3.37 to 5.67)	45.13 (7.50)	46.41 (7.19)	0.872 (0.743–0.938)	2.58 (–3.79 to 6.35)
Dorsal side forearm	42.20 (6.86)	42.16 (6.87)	0.867 (0.739–0.935)	2.46 (–4.78 to 4.86)	42.10 (7.10)	42.10 (6.97)	0.820 (0.655–0.910)	2.94 (–5.75 to 5.75)
Elbow	36.76 (5.14)	34.39 (4.96)	0.766 (0.292–0.909)	2.4 (–2.34 to 7.08)	36.69 (4.69)	34.05 (4.93)	0.736 (0.152–0.902)	2.43 (–2.12 to 7.4)
Ventral side upper arm	37.52 (5.37)	38.77 (5.05)	0.889 (0.718–0.952)	1.71 (–2.1 to 4.6)	37.06 (5.49)	38.54 (4.90)	0.828 (0.612–0.921)	2.12 (–2.67 to 5.63)
Dorsal side upper arm	36.51 (4.90)	38.13 (4.80)	0.867 (0.739–0.935)	1.74 (–1.79 to 5.03)	36.63 (4.81)	38.00 (5.06)	0.783 (0.566–0.894)	2.26 (–3.01 to 5.83)
Lateral shoulder (Deltoid muscle)	46.54 (4.84)	45.45 (5.53)	0.841 (0.681–0.923)	2.03 (–2.89 to 5.07)	46.35 (5.06)	45.46 (5.54)	0.834 (0.681–0.918)	2.12 (–3.27 to 5.05)
Breast/ventral trunk region	43.16 (6.49)	43.19 (8.05)	0.768 (0.565–0.882)	3.44 (–6.73 to 6.77)	42.67 (6.53)	42.84 (8.28)	0.736 (0.514–0.865)	3.74 (–7.16 to 7.50)
Lateral trunk	45.60 (4.89)	45.62 (4.36)	0.751 (0.537–0.873)	2.27 (–4.43 to 4.47)	45.06 (4.87)	45.81 (4.54)	0.744 (0.533–0.869)	2.34 (–3.84 to 5.34)

Inter-rater reliability MMDC device

Results regarding the inter-rater reliability (ICC, SEM) of the MMDC device after a single measurement, as well as after multiple measures on each of the nine measurement points, are presented in Table 5. Results regarding inter-rater reliability (ICC, SEM) of the MMDC device after calculating the interarm PWC% ratio based on a single measurement, as well as based on multiple measures on each measurement point, are shown in Table 6.

Analysis of the multiple measurements at the edematous limb showed strong to very strong reliability (ICCs ≥0.75) of all measurement points, except at the ventral side of the forearm (ICC 0.606), and lateral trunk (ICC 0.726), which showed moderate reliability. The statistical analysis of the single measurements revealed strong to very strong reliability (ICCs ≥0.75) of all measurement points, except at the elbow (ICC 0.636), dorsal side of the upper arm (ICC 0.711), and lateral trunk (ICC 0.643) (moderate reliability).

Analysis of the multiple measures at the nonedematous limb yielded strong inter-rater reliability for all measurement points except for the hand (ICC 0.665) (moderate reliability). The statistical analysis of the single measurements revealed strong inter-rater reliability of all measurement points except for the hand (ICC 0.616), elbow (ICC 0.736), breast (ICC 0.736), and lateral trunk (ICC 0.744) (moderate reliability).

Values of the interarm PWC ratios based on multiple measures showed strong inter-rater reliability for the measurement points at the hand (ICC 0.752), ventral side of the upper arm (ICC 0.862), and lateral trunk (ICC 0.760). Similarly, analysis of the interarm PWC ratios based on single measurements revealed strong inter-rater reliability for the measurement points at the hand (ICC 0.775), ventral side of the upper arm (ICC 0.847), and lateral trunk (ICC 0.787).

Intrarater agreement pitting test

The statistical analysis of the pitting test values showed an almost perfect intrarater agreement ($K > 0.81$) for the majority of the measurement points (Table 7). The highest kappa coefficients were found for the ventral side of the forearm ($K = 0.866$) and the elbow ($K = 0.866$). Hundred percent agreement was achieved at the lateral shoulder. The lowest kappa coefficient was shown at the breast ($K = 0.694$), suggesting substantial agreement (83.3%). With exception of this latter, all percentages of agreement were above 90%.

Inter-rater agreement pitting test

Overall, the statistical analysis of the pitting test showed a slight to fair inter-rater agreement, with exception of the measurement points at the elbow and the breast which showed no agreement ($K < 0.00$) (Table 8). The highest kappa coefficient was found for the hand ($K = 0.304$) and was classified as a fair agreement. Similar to the results of the intrarater agreement, the highest percentage of inter-rater agreement was shown at the lateral shoulder (96.7%), this time together with the lateral trunk (96.7%). Lowest percentage of agreement was for the measurement point at the elbow (26.7%).

Discussion

The widespread use of the pitting test and the more recently upcoming application of the MMDC device in clinical practice and research, together with the existing gaps in evidence regarding their clinimetric properties, underline the importance of this study. Both tools are easily applicable, noninvasive, and useful for assessing changes in % local tissue water.

Due to the scarce amount of evidence on reliability of the MMDC device, it is difficult to compare the results of this study with previous findings. Only one study was found, in which reliability of TDC measures was investigated on edematous upper limbs. Czerniec et al. examined intrarater reliability of the MMDC device with different probe sizes (extra small, small, and medium) on the upper limbs of 24 participants, 20 of whom with BCRL and 4 without lymphedema. ICC values of two averaged TDC measures with medium probe size at the self-reported most affected region (upper or lower arm) of the edematous limb ranged between 0.82 and 0.96, which is comparable to our results.[26] ICC calculations on interarm TDC ratio results were not performed. Recently, Mayrovitz et al. investigated test–retest reliability of absolute TDC measures and interlimb TDC ratios at three locations on healthy upper limbs, using the compact probe and multiprobe of the MoistureMeterD device.[14] Although they did not include patients with BCRL, their results were similar to our findings at the nonedematous limb, with exception of the hand, which showed moderate reliability in our study (ICC = 0.665 vs. 0.945).[14] Also, their results were comparable with their earlier findings on inter-rater reliability of the MoistureMeterD device on different sites at the upper nonedematous limb of patients newly diagnosed with breast cancer.[6] Despite the fact that some of these previous studies used a MoistureMeterD instead of a MMDC device,[24,26] and consequently, the outcomes were reported in absolute TDC values instead of PWC% values, their results were comparable with the findings of our study at the nonedematous limb.

Both absolute PWC% values and interarm PWC% ratios have shown to be meaningful tools to evaluate the effects of therapeutic interventions.[9] In general, results of our study yielded lower interarm ratio ICC values compared to absolute PWC% value ICC results. Although we cannot directly compare our findings due to a different study cohort, this aspect was also observed in the recent study of Mayrovitz et al. in nonedematous limbs.[14] Nevertheless, they suggested that when the interarm ratio is the parameter of interest, studies using different probes would yield analogous results that can be compared, as confirmed by their findings.[14]

Depending on the measurement point, results of our reliability study ranged from moderate to very strong. In general, this revealed that the edematous and nonedematous limb could be evaluated during follow-up in a reliable way both by the same assessor as well as by different assessors.

In our study, for seven out of nine locations, intrarater ICCs and SEMs were comparable between single and multiple measures. At the ventral side of the forearm, intrarater reliability evolved from moderate to strong when using multiple measures instead of single measures. At the lateral shoulder, intrarater reliability evolved from strong to very strong when using multiple measurements instead of single

TABLE 6. INTER-RATER RELIABILITY OF THE INTERARM PERCENTAGE OF WATER CONTENT RATIO

| | Interarm PWC% ratio | | | | | | | |
| | Multiple measurements | | | | Single measurements | | | |
	Rater 1, interarm PWC% ratio (SD)	Rater 1, interarm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)	Rater 1, interarm PWC% ratio (SD)	Rater 1, interarm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)
Hand	1.14 (0.20)	1.11 (0.16)	0.752 (0.546–0.873)	0.09 (0.51–0.87)	1.17 (0.25)	1.14 (0.21)	0.775 (0.580–0.886)	0.11 (0.48–0.90)
Ventral side forearm	1.35 (0.32)	1.31 (0.15)	0.186 (−0.188 to 0.510)	0.21 (0.73–1.57)	1.39 (0.22)	1.32 (0.14)	0.406 (0.072–0.664)	0.14 (0.88–1.42)
Dorsal side forearm	1.34 (0.19)	1.33 (0.18)	0.719 (0.487–0.856)	0.1 (−0.15 to 0.23)	1.34 (0.21)	1.33 (0.20)	0.617 (0.332–0.798)	0.13 (−0.21 to 0.29)
Elbow	1.44 (0.22)	1.49 (0.29)	0.662 (0.407–0.823)	0.15 (2.08–2.66)	1.44 (0.20)	1.49 (0.3)	0.615 (0.339–0.795)	0.16 (2.07–2.67)
Ventral side upper arm	1.20 (0.21)	1.22 (0.22)	0.862 (0.731–0.931)	0.08 (1.09–1.41)	1.21 (0.22)	1.22 (0.21)	0.847 (0.703–0.924)	0.08 (1.09–1.41)
Dorsal side upper arm	0.99 (0.13)	1.27 (0.19)	0.167 (−0.092 to 0.472)	0.14 (1.34–1.9)	1.21 (0.16)	1.26 (0.20)	0.663 (0.404–0.823)	0.1 (1.42–1.82)
Lateral shoulder (Deltoid muscle)	1.00 (0.08)	1.04 (0.09)	0.470 (0.152–0.704)	0.06 (0.97–1.21)	1.00 (0.09)	1.03 (0.09)	0.410 (0.078–0.664)	0.07 (0.95–1.23)
Breast/ventral trunk region	1.20 (0.22)	1.22 (0.25)	0.700 (0.460–0.845)	0.14 (−0.08 to 0.12)	1.21 (0.22)	1.24 (0.28)	0.644 (0.377–0.813)	0.15 (−0.08 to 0.12)
Lateral trunk	1.06 (0.11)	1.06 (0.10)	0.760 (0.553–0.878)	0.05 (−0.08 to 0.12)	1.07 (0.11)	1.05 (0.11)	0.787 (0.603–0.892)	0.05 (−0.08 to 0.12)

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TABLE 7. INTRA-RATER AGREEMENT PITTING TEST (N=30)

Pitting test Intrarater	Score[a]	Rater 1 (No.)	Rater 1 (No.)	% Agreement	Cohen's kappa
Edematous limb					
Hand	Score 0	25	22	90	0.710
	Score 1	5	8		
Ventral side forearm	Score 0	2	1	96.7	0.866
	Score 1	19	19		
	Score 2	9	10		
Dorsal side forearm	Score 0	3	3	93.3	0.855
	Score 1	21	21		
	Score 2	6	6		
Elbow	Score 0	16	16	93.3	0.866
	Score 1	14	14		
Ventral side upper arm	Score 0	28	27	96.7	0.783
	Score 1	2	3		
Dorsal side upper arm	Score 0	24	22	93.3	0.815
	Score 1	6	8		
Lateral shoulder (Deltoid muscle)	Score 0	30	30	100	/
Breast/ventral trunk region	Score 0	10	10	83.3	0.693
	Score 1	18	17		
	Score 2	2	3		
Lateral trunk	Score 0	29	30	96.7	/
	Score 1	1			

[a]Score 0=no clinical pitting edema; score 1=slight/doubtful pitting edema; score 2=noticeably pitting edema.

measures. Likewise, when comparing intrarater reliability of interarm PWC% ratios, one can notice that results (ICC, SEM) based on single and multiple measures were similar. Remarkably, intrarater reliability deteriorated from very strong to strong at the ventral side of the upper arm, from strong to weak at the dorsal side of the upper arm, and from moderate to weak at the ventral side of the forearm when using multiple measurements instead of single measures. Concerning the results for intrarater reliability as well as interrater reliability, the ICC value at the dorsal side of the upper arm was noticeably higher when it was based on a single measurement instead of multiple measures.

TABLE 8. INTER-RATER AGREEMENT PITTING TEST (N=30)

Pitting test Inter-rater	Score[a]	Rater 1 (No.)	Rater 2 (No.)	% Agreement	Cohen's kappa
Edematous limb					
Hand	Score 0	25	21	73.3	0.304
	Score 1	5	6		
	Score 2		3		
Ventral side forearm	Score 0	2	1	56.7	0.300
	Score 1	19	8		
	Score 2	9	21		
Dorsal side forearm	Score 0	3	2	40	0.151
	Score 1	21	6		
	Score 2	6	22		
Elbow	Score 0	16	11	26.7	−0.009
	Score 1	14	5		
	Score 2		14		
Ventral side upper arm	Score 0	28	22	76.7	0.234
	Score 1	2	5		
	Score 2		3		
Dorsal side upper arm	Score 0	24	16	50	0.038
	Score 1	6	8		
	Score 2		6		
Lateral shoulder (Deltoid muscle)	Score 0	30	29	96.7	/
	Score 1		1		
Breast/ventral trunk region	Score 0	10	13	36.7	−0.048
	Score 1	18	12		
	Score 2	2	5		
Lateral trunk	Score 0	29	30	96.7	/
	Score 1	1			

[a]Score 0=no clinical pitting edema; score 1=slight/doubtful pitting edema; score 2=noticeably pitting.

Since our results showed that it seems sufficient to measure each reference point only once instead of in triplicate, evaluating BCRL with this tool can be even more time-efficient. These findings are confirmed by recent results of Mayrovitz et al.,[14] who conducted a study to investigate whether single measurements of reference points are sufficient for evaluating BCRL. Thirty women were recruited, and TDC was measured in triplicate bilaterally at the ventral side of the forearm and at the hand palm. The agreement in absolute TDC values and interarm ratios was evaluated for assessments made using only the first TDC measurement, the average of duplicates and the standard triplicate. Results suggested that in upper limbs, useful TDC data may be obtained using single measurements.[14]

Results concerning the pitting test, presented a good to very good intrarater agreement, with most measurement points showing almost perfect agreement (K between 0.82 and 0.87). At the lateral shoulder and lateral trunk, a high percentage of agreement together with the absence of kappa values could be noticed. The lack of variation in measurement results, due to the absence of pitting edema presented in these areas within our study sample, impeded the calculation of kappa values for these points.

In contrast to the very good intrarater agreement, overall rather low kappa values question the inter-rater agreement of this test. The inconsistencies such as the area, amount and duration of applied pressure between raters, could explain these results as described by Sanderson et al.[29] Although guidelines are advocating for the use of this test in the evaluation of lymphedema,[28] even the most fundamental components of the pitting test, such as the required amount and area of pressure, have not been consistently described in literature.[36] Consequently, this leads to a different interpretation of the test results among different assessors: what is the difference between ''noticeable pitting'' and ''slight/doubtful'' pitting?

The complex and sometimes varying skin tissue composition at the breast between patients due to surgery or radiotherapy could be a reason for the lowest kappa value at this location (-0.048). The measurement point at the hand, revealing a fair kappa (0.304) and 73% of agreement, indicated the highest inter-rater agreement. Given the paucity of research literature on this topic, we were unable to compare our findings.

Despite the fact that it is outside the scope of this study, it should be mentioned that (especially regarding the pitting test) it is uncertain which part of the skin is being measured. For the MMDC device, the effective penetration depth is about 2 mm.[14] This effective penetration depth has been defined as the depth at which the incident energy falls to 37% of its surface value.[14,18] Although the arm has a mean skin thickness of 2.23 mm (95% CI 2.18–2.28).[37]

When applying the pitting test, the indentation depths may vary but are likely to include both the epidermis and subcutis. Knowledge about what exactly is being measured is lacking.

Strengths and limitations

The current study has several strengths. First, since we analyzed reliability of the MMDC device by measuring both the edematous and the nonedematous limb, our results can be extrapolated to a population with lymphedema as well as to a healthy population or to a patient population without clinical representation of lymphedema. Second, this study used nine different measurement points spread over the entire upper limb, including the breast and lateral trunk, which are important locations as well that should not be neglected in this population.[38] This is in contrast to most of the (few available) previous studies, which only focused on a small number of measurement points such as the hand and ventral side of the forearm. Third, to eliminate any risk for recall bias between the measurements, the assessor was supported by an assistant writing down the values and, consequently, ensuring blinding of the data. A possible limitation of the study may be the relatively small number of participants, which might have lowered the variability between participants. However, as stated by Shrout and Fleiss, researchers should try to obtain at least 30 heterogeneous subjects for reliability studies, which was established in this study.[34] Furthermore, the applied procedure of the pitting test did not include an indication for the amount of pressure that was given, hindering the standardization of the test regarding this aspect. However, a 1-hour training moment between experienced assessors was organized improving standardization of the measurement procedure considering patient position, pressure area, and pressure time for this test.

Clinical implications and future research

This study showed that the MMDC device can reliably be used to evaluate patients with BCRL during follow-up, both by the same assessor as by different assessors. When single measurements are performed by the same assessor, a test variation of more than 5.23 PWC% (or 0.17 in case interlimb ratios are calculated) should be considered as a change in local tissue water, exceeding the measurement error at the edematous limb. In case the measurement is performed by different assessors, a test variation of more than 5.34 PWC% (or 0.16 in case interlimb ratios are calculated) exceeds the area of measurement error. Consequently, if two MMDC measurements differ more than 5.23 PWC% or 5.34 PWC%, respectively, the difference can be interpreted as an identifiable difference in local tissue water, which is not related to a SEM.

In addition, this study showed that the pitting test has a very strong intrarater agreement at well-nigh all measurement points, but a rather questionable inter-rater agreement, especially at the medial elbow and the breast. Therefore, follow-up evaluations over time should be performed by the same assessor per patient.

When interpreting these results, one should keep in mind that in both methods different parts of the skin are being assessed. MMDC measurements are mainly focused on the evaluation of epidermal edema (up to 2 mm) with only partly giving information regarding the subcutaneous area, whereas the pitting test does provide information concerning both skin layers. Further research should focus on the amount of pressure necessary to evaluate the skin tissue correctly and to improve the standardization of the pitting test. More evidence regarding what exactly is being measured up to which depth is needed. In addition, after standardization of this test is completed, future studies that examine concurrent validity of the pitting test and the MMDC device, for instance by comparing obtained results with ultrasound images representing

skin thickness, are warranted to increase the clinical relevance of both tools.

Conclusion

In summary, the overall positive findings support the use of MMDC device as a reliable tool for evaluating local tissue water in patients with BCRL, both by the same assessor as well as by different assessors. Absolute PWC% measures usually showed stronger reliability than interarm PWC% ratios. In addition, reliability of single and multiple PWC% measures yielded comparable results at most measurement points. Furthermore, positive results regarding the pitting test applied by the same assessor empower the use of this easy and quick test. However, rather low kappa values regarding the inter-rater reliability question the reproducibility of the pitting test between different assessors.

The MMDC device and the pitting test as well are useful tools in the clinical evaluation of BCRL over time. Further research into the concurrent validity of both tools is warranted.

Clinical Trial Registration Number

The study makes part of a double-blind, multicenter, randomized controlled trial (EFforT-BCRL trial), which is registered in clinicaltrials.gov (NCT02609724). CME reference S58689, EudraCT number 2015-004822-33.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Tessa De Vrieze, PT, MT
Department of Rehabilitation Sciences
KU Leuven–University of Leuven
O&N IV Herestraat 49, Box 1510
3000 Leuven
Belgium

E-mail: tessa.devrieze@kuleuven.be