Lower limb lymphedema: evaluation of measurements and exercise

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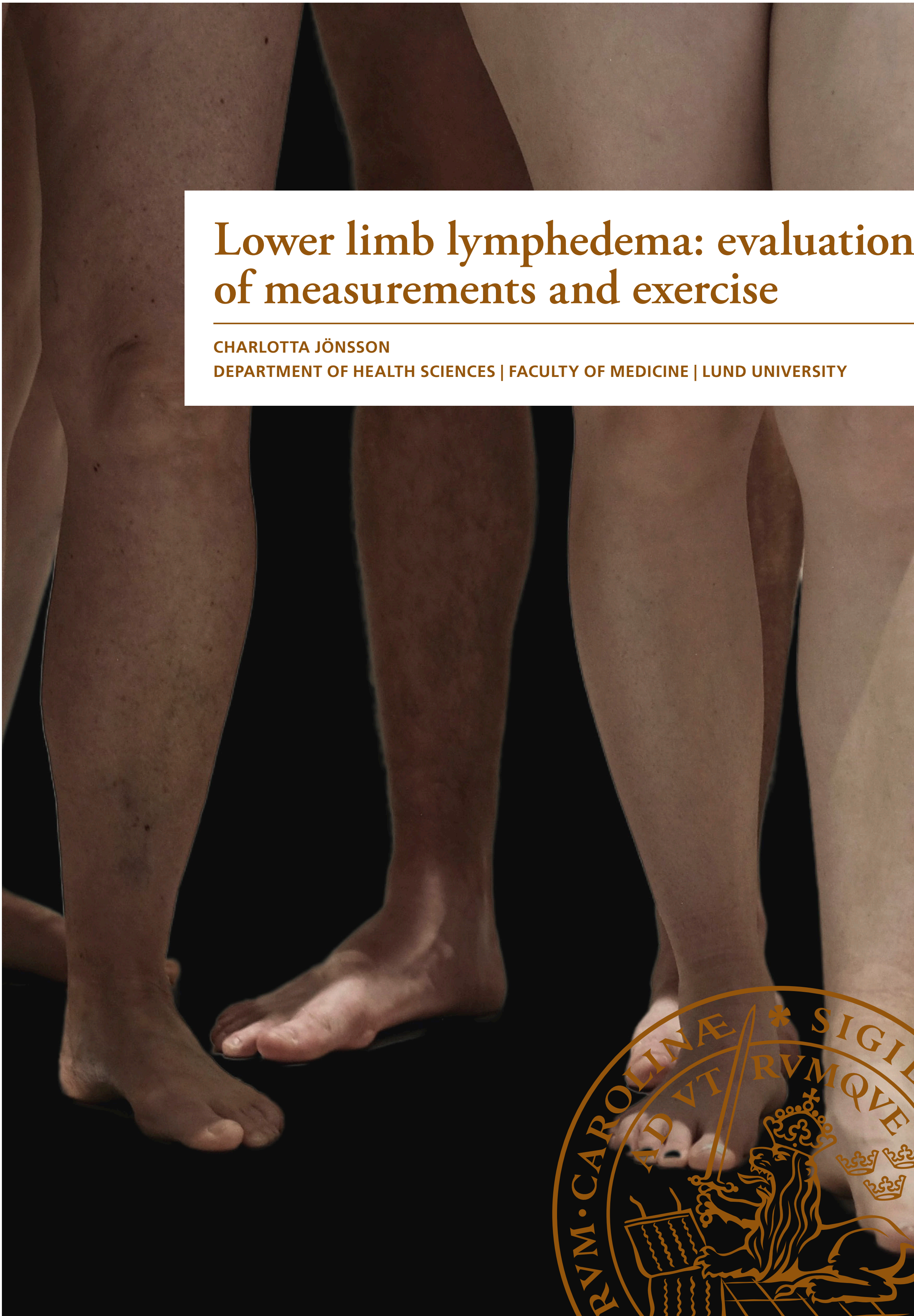

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Charlotta Jönsson

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD)
at the Faculty of Medicine at Lund University to be publicly defended on
the 30 of November 2023 at 9.00 a.m in Belfragsalen, BMC, Klinikgatan 32, Lund

Faculty opponent
Professor Karin Ahlberg, Sahlgrenska Akademin,
University of Gothenburg.

Organization: LUND UNIVERSITY

Document name: Doctoral dissertation

Date of issue: 2023-11-30

Author(s): Charlotta Jönsson

Sponsoring organization:

Title and subtitle: Lower limb lymphedema: evaluation of measurements and exercise

Abstract

Several measurements can be used to assess lower limb lymphedema (LLL), but knowledge of their reliability is limited. Moderate intensity exercise has many health benefits, but there is lack of knowledge about its benefits and feasibility in persons with mild to moderate LLL.

The overall aim of this thesis was to increase the knowledge about appropriate measurement methods to assess lymphedema in persons with primary or secondary LLL, to evaluate the test-retest reliability of those measurements and the benefit and feasibility of moderate intensity bicycling exercise.

In study I, 61 healthy persons were measured twice, two weeks apart with CMs every 4th cm for volume and tissue dielectric constant (TDC) at 14 points for local tissue water. In study II, 42 persons with LLL were measured twice, two weeks apart with CMs, TDC and arm-leg impedance ratio for extracellular fluid (ECF). Test-retest reliability including measurement errors were evaluated. In study III, CMs every 4th cm (V4), every 8th cm (V8) and every 12th cm (V12) were used. The agreement between measurements was evaluated with Intraclass Correlation Coefficients (ICCs), Bland-Altman graphs, and test-retest reliability with the same statistics as in study I and II. In study IV, 33 persons with LLL were randomized to moderate intensity bicycling exercise (intervention group, IG, n=21), 3-5 times per week for 8 weeks or usual daily activity (control group, CG, n=12). Primary outcomes were volume, local tissue water and ECF. Secondary outcomes were physical fitness, health-related quality of life (HRQOL) and lymphedema-related disability. Feasibility was evaluated with compliance and adverse events. Nonparametric statistical analyses were performed.

In healthy persons, reliability for CMs was high and measurement errors low. For TDC, reliability was fair to excellent in women and poor to excellent in men. Measurement errors were acceptable except three points in men (study I). In persons with LLL, reliability for CMs was high and measurement errors low. For TDC, reliability was fair to excellent and measurement errors acceptable. For impedance ratio, reliability was high and measurement errors acceptable (study II). In study III, the agreement was higher between the V4 and V8 methods than between the V4 and V12. Reliability was high for all three methods and measurement errors low. Twenty-seven participants (IG, n=16, CG, n=11) completed study IV. A significant difference between the groups (p=0.05) regarding lymphedema-related disability in favour of the IG was found, but not in any other outcomes. Within the IG, significant decrease in ECF R(0) ($p<0.05$) and improvements in TDC ($p<0.05$), VO2max ($p<0.05$) and HRQOL ($p<0.05$) were found, but no changes in the CG. The exercise protocol was well tolerated and adhered to, with few adverse events.

In conclusion, several measurement methods for lower limbs in healthy persons and in persons with LLL are reliable and recommended. The V8 method can replace the V4 method to save time. Moderate intensity bicycling exercise is beneficial and feasible in persons with LLL.

Key words: lower extremity, healthy volunteers, lower limb lymphedema, intra-rater reliability, circumferential measurements, outcome measures, bicycling exercise, moderate intensity

Classification system and/or index terms (if any)

Supplementary bibliographical information

Language English

ISSN and key title: 1652-8220

ISBN: 978-91-8021-479-7

Recipient's notes

Number of pages: 89

Price

Security classification

Signature

Date 2023-10-19

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ISBN 978-91-8021-479-7
ISSN 1652-8220
Lund University, Faculty of Medicine Doctoral Dissertation Series 2023:137

Printed in Sweden by Media-Tryck, Lund University
Lund 2023

This thesis is dedicated to all patients
who have inspired me to increased knowledge

Table of Contents

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In conclusion, several measurement methods for lower limbs in healthy persons and in persons with LLL are reliable and recommended. The V8 method can replace the V4 method to save time. Moderate intensity bicycling exercise is beneficial and feasible in person with LLL.

List of Papers

This thesis is based on the following papers:

I. Jönsson C, Bjurberg M, Brogårdh C, Johansson K. Test-retest reliability of volume and local tissue water measurements in lower limbs of healthy women and men. Lymphat Res Biol. 2020 ;18 :261-269. doi: 10.1089/lrb.2019.0044.

II. Jönsson C, Johansson K, Bjurberg M, Brogårdh C. Impedance of extracellular fluid, volume and local tissue water can be reliably measured in people with lower limb lymphedema. Phys Ther. 2022; 102:pzac025. doi: 10.1093/ptj/pzac025.

III. Jönsson C, Johansson K, Bjurberg M, Brogårdh C. Circumferential measurements to calculate lower limb volume in persons with lymphedema: What segment length is to be recommended? Lymphat Res Biol. 2023 ;21 :275-282. doi: 10.1089/lrb.2022.0032

IV. Jönsson C, Johansson K, Bjurberg M, Brogårdh C. Bicycle exercise in persons with lower limb lymphedema: A pilot randomized controlled trial. In manuscript.

Svensk sammanfattning

Lymfödem innebär en svullnad i vävnaden på grund av nedsatt funktion i lymfsystemet och är en vanlig biverkning till cancerbehandling med omfattande lymfkörtelkirurgi och/ eller strålbehandling, men funktionsnedsättningen kan också vara medfödd. Flera metoder kan användas för att mäta benlymfödem, men kunskapen om tillförlitligheten (reliabiliteten) i metoderna är begränsad. Träning på måttlig intensitet har många hälsovinster, men kunskaperna om fördelarna och genomförbarheten hos personer med små och måttliga benlymfödem är begränsad.

Det övergripande syftet med denna avhandling var att öka kunskapen om lämpliga mätmetoder för att bedöma lymfödem i benen hos personer med medfödd svaghet i lymfsystemet eller som behandlats för olika typer av cancerformer, att utvärdera mätmetodernas tillförlitlighet och mätfel (reliabilitet) samt nyttan och genomförbarheten av cykelträning på måttlig intensitet.

I studie I mättes 61 friska personer vid två tillfällen med två veckor emellan med omkrets var 4:e cm för volym och tissue dielectric constant (TDC) på 14 punkter för lokal vävnadsvätska. I studie II mättes 42 personer med benlymfödem vid två tillfällen med två veckor emellan med omkrets, TDC och arm-ben kvot för impedansen i extracellulär vätska (ECF). Test-retest reliabiliteten utvärderades med intraklasskorrelationskoefficient (ICC), förändringar i medelvärdet och mätfelets storlek. I studie III användes omkretsmått var 4:e cm (V4 metoden), var 8:e cm (V8 metoden) och var 12:e cm (V12 metoden) för beräkning av volym. Överensstämmelsen mellan mätmetoderna utvärderades med ICC, Bland-Altman graferna och reliabilitet med samma analysmetoder som i studie I och II. I studie IV randomiserades 33 deltagare med benlymfödem till hembaserad cykelträning på måttlig nivå (interventionsgrupp, n=21) under 8 veckor, respektive vanliga dagliga aktiviteter (kontrollgrupp, n=12). Träningen skedde 3–5 gånger per vecka, 30–60 minuter/ gång med korta kontroller var 14:e dag. Primära utfallsmått var benlymfödemstatus (volym, lokal vävnadsvätska och impedans av ECF). Sekundära utfallsmått var kondition, hälsorelaterad livskvalitet och upplevd lymfödemrelaterad funktionsnedsättning. Genomförbarheten utvärderades med följsamhet och biverkningar. Icke-parametrisk statistik användes.

Hos friska personer var reliabiliteten för omkretsmätning utmärkt och mätfelen små. För TDC var reliabiliteten god till utmärkt hos kvinnor och dålig till utmärkt hos män. Mätfelen var acceptabla, förutom i tre punkter hos män (studie I). Hos personer med benlymfödem var reliabiliteten för omkretsmätning utmärkt och mätfelen små. För TDC var reliabiliteten god till utmärkt och mätfelen acceptabla. För impedanskvoten var reliabiliteten utmärkt och mätfelen acceptabla. I studie III var överensstämmelsen högre mellan V4 och V8 än mellan V4 och V12. Reliabiliteten var utmärkt för alla tre metoderna och mätfelen små. Tjugo-sju personer (interventionsgrupp n=16, kontrollgrupp n=11) fullföljde studie IV. En signifikant skillnad mellan grupperna ($p=0.05$) avseende upplevd lymfödemrelaterad funktionsnedsättning till förmån för interventionsgruppen fanns, det fanns ingen skillnad i andra utfallsmått. I interventionsgruppen minskade ECF R(0) ($p<0.05$), medan lokal vävnadsvätska ($p<0.05$), kondition ($p<0.05$) och livskvalitet ($p<0.05$) förbättrades. Inga förändringar uppmättes i kontrollgruppen. Träningsprotokollet följdes och tolererades väl, med få biverkningar.

Sammanfattningsvis är flera mätmetoder för benmätning reliabla hos friska personer och personer med benlymfödem. V8 metoden kan ersätta V4 metoden för att spara tid. Cykelträning på måttlig intensitet är välgörande och genomförbart hos personer med benlymfödem.

Abbreviations

BIS	Bio Impedance Spectroscopy
BMI	Body Mass Index
CI	Confidence Interval
CG	Control Group
CM	Circumferential Measurement
ECF	Extra Cellular Fluid
HRQOL	Health-Related Quality of Life
HRR	Heart Rate Reserve
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Function, Disability and Health
IG	Intervention Group
LLL	Lower Limb Lymphedema
LOA	Limits of Agreement
LyQLI	Lymphedema Quality of Life Inventory
PA	Physical Activity
PWC	Percentage Water Content
RCT	Randomized Controlled Trial
RPE	Ratings of Perceived Exertion
SEM	Standard Error of Measurement
SRD	Smallest Real Difference
TDC	Tissue Dielectric Constant
VAS	Visual Analogue Scale
WHO	World Health Organisation

Thesis at a glance

Aims	Methods	Results	Conclusions
Paper 1: To evaluate test-retest reliability of circumferential measurements (CMs) and tissue dielectric constant (TDC) in healthy women and men and to define limits that indicate changes over time for a group of subjects and single subjects.	Thirty-three women and 28 men were measured twice, 2 weeks apart. Volume and TDC in 14 points were evaluated by the intraclass correlation coefficient (ICC 2.1), changes in the mean and measurement errors.	For CMs, high reliability, and low measurement errors. For TDC, fair to excellent reliability in women, poor to excellent in men. Acceptable measurement errors in women and in 11 points in men.	CMs and TDC measurements are reliable in healthy women and men, both methods can be recommended.
Paper 2: To evaluate the test-retest reliability of impedance ratio of extracellular fluid (ECF), CMs and TDC in persons with unilateral or bilateral lower limb lymphedema (LLL) and measurement errors for a group of persons and for a single individual.	Forty-two persons with mild to moderate LLL were measured twice, two weeks apart. Impedance ratio, CMs and TDC measurements were evaluated by ICC 2.1, changes in the mean and measurement errors.	For impedance ratios, high reliability and acceptable measurement errors. For CMs, high reliability and low measurement errors. For TDC, fair to excellent reliability and acceptable measurement errors.	Impedance ratios, CMs and TDC measurements are reliable in persons with LLL. Acceptable measurement errors indicate that real, clinical changes in lymphedema can be measured.
Paper 3: To establish the agreement between lower limb volume measurements derived from CMs every 4thcm (reference standard) (V4), every 8thcm (V8), and every 12thcm (12) and to evaluate the test-retest reliability for the three methods in LLL.	Forty-two persons with LLL were measured twice, two weeks apart. Agreement between the measurements was evaluated by ICC3.1 and Bland-Altman graphs. Reliability was evaluated by ICC 2.1, changes in the mean and measurement errors.	The agreement was slightly higher between the V4 and V8 method than between the V4 and V12. High reliability and low measurement errors for all methods.	Higher agreement between the V4 and V8 than between the V4 and V12 and the high test-retest reliability in all three methods support the V8 method to replace the V4 in the clinic.
Paper 4: To investigate the efficacy of bicycling exercise at a moderate intensity compared to usual daily activity and the feasibility of the exercise in persons with LLL.	Thirty-three persons were randomized to an intervention group (IG) or control group. The IG performed home-based bicycling 3-5 times a week for 8 wks. Primary outcomes were volume, local tissue water and ECF. Secondary outcomes were physical fitness, HRQOL and perceived lymphedema-related disability. Feasibility by retention, adherence, and adverse events.	A significant change between groups in lymphedema related disability in favour of the IG. No other differences between the groups. In the IG significant decrease of ECF, improvements in local tissue water, physical fitness and HRQOL. The protocol was well tolerated and few adverse events.	Bicycling at moderate intensity is feasible and improves local tissue water, lymphedema related disability, physical fitness, HRQOL in persons with LLL. Regular check-ups for volume control and guidance can be supportive.

Introduction

Lymphedema is manifested as swelling in the peripheral tissue caused by an insufficiency in lymph drainage. Normally there is a balance between fluid input from the capillaries and lymph drainage output. Under normal conditions, the lymphatic drainage capacity by far exceeds the production of filtrate to the tissue (1). In developed countries lymphedema is mostly associated with cancer treatment that causes disruption of lymph flow because of extensive surgery with lymph node dissection or the combination of surgery and radiation (2). Lower limb lymphedema (LLL) may also be developed due to congenital lymphatic dysfunction. Irrespective of aetiology lymphedema is considered a chronic condition.

In LLL management, measurements are regularly obtained for different purposes such as to diagnose a condition, to plan an appropriate treatment, to assess short term effects or long-term effects of an intervention or self-care. For repeated measurements it is important to consider reliability and measurement errors (3, 4). Overall, there is very limited knowledge about reliable measurements in persons with LLL (5).

For persons with lymphedema physical activity is part of the self-care, but the advice about physical activity and exercise have been very inconsistent for many years. Historically, there has been an assumption that the increased circulation caused by exercise may have a negative impact on the already impaired lymphatic system. During the last 20 years, research has provided convincing evidence that aerobic and resistance exercise do not worsen the lymphedema at least for those with breast cancer related upper-limb lymphedema (6). For persons with LLL the knowledge about the effects of exercise is still very limited.

The lymphatic system

The lymphatic system consists of lymphoid organs (including lymph nodes) and lymphatic vessels and is a unidirectional vascular system draining fluid from the tissue back to the blood stream (1) (Figure 1). The initial lymphatic capillaries start blindly in the tissue. These capillaries are highly permeable to interstitial fluid and when the fluid enters these capillaries it is called lymph. By changes in hydrostatic and osmotic pressure due to skeletal muscle contractions, arterial pulsation, breathing, intestinal peristalsis, and external body compression the lymph is transported from the initial lymphatic capillaries into the precollecting and collecting lymphatic vessels (1). These vessels contain valves and smooth muscle cells which will contract the vessels spontaneously, functioning as small intrinsic pumps called lymphangions, to move lymph forward and prevent backflow of the lymph (2, 7) (Figure 2).

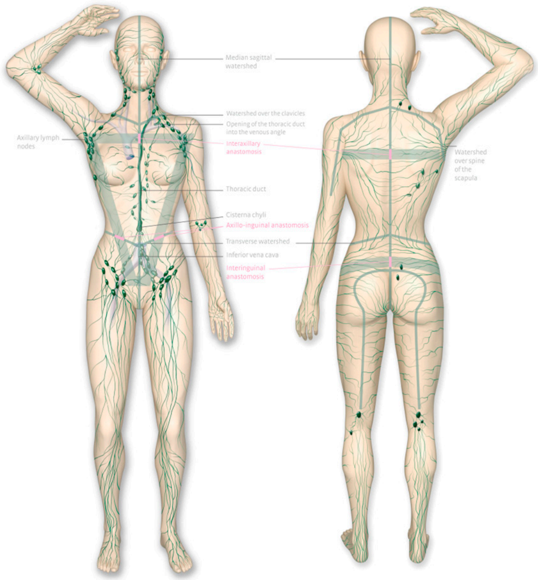

Figure 1. Illustration of lymphatic vessels and lymph nodes in the lymphatic system. © medi

The lymph will be transported further on towards lymph nodes and finally to the larger lymphatic vessels, (the cisterna chyli, the thoracic duct and the right lymphatic duct) where the lymph returns to the venous circulation system near the neck, close to the jugular vein and the subclavian vein (1).

In the extremities there are both superficial and deeper lymphatic vessels, which in general connect only in the proximal body regions (2). The lymph vessels have an important role as a conduit system transporting salt, proteins, cells (immune cells and cell debris) back to the blood stream for recycling or for final disposal by the lymphatic system. Research has also shown that the lymphatic system besides immunity and immunosurveillance, also has an active role transporting nutrients to tissues, fat absorption in the gut and transportation of peripheral fat. One of the main functions of the lymphatic system is general body fluid homeostasis, thus not only interstitial fluid homeostasis (1).

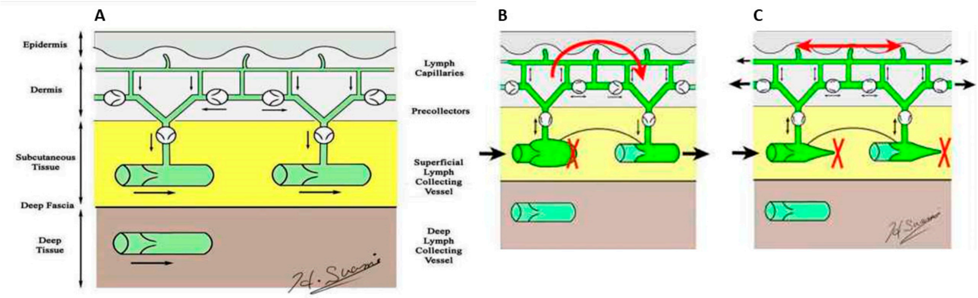

Figure 2. Schematic diagram of the peripheral lymphatic system (A). Structural changes in the lymphatic system creating alternative pathways for the lymph in persons at risk of cancer related lymphedema (B and C). Reproduced with permission of Hiroo Suami.

Pathophysiology

Lymphedema is a pathophysiologic condition in the lymphatic system, leading to build-up of lymph in the peripheral tissues caused by injury to the lymphatic system because of oncological treatment, obstruction, infection, or congenital defects (8). The increase of lymph will lead to responses in the lymphatic system such as alternative pathways for the lymph (Figure 2, B and C), regenerating lymphatic vessels or detouring lymph via the deep lymphatic system (2). The onset of cancer related LLL seems to vary from a few months after surgery (9) to several years later (10). The swelling will gradually become chronic due to low graded chronic inflammation, adipose deposition, and tissue fibrosis with secondary skin changes i.e., hyperkeratosis (11). For some persons the changes in limb volume or tissue changes are small over very long periods of time whereas for others the progression is rapid with disabling swelling and physiologic changes (11). A slower progression may be apparent with shorter time from onset to start of treatment (12), but with appropriate management the oedema may be alleviated (13).

Lower limb lymphedema

Traditionally lymphedema is divided into primary and secondary lymphedema depending on the cause to the swelling (Figure 3). Primary LLL is caused by congenital defects to the lymphatic system resulting from genetics or developmental abnormalities (14). It can also be part of a syndrome (14) but for most persons the lymphedema will be manifested as malformation of the lymph vessels in an extremity (11). Even though the malformation of the lymphatic vessels is present at birth the onset of swelling is more prevalent later in childhood or even later in life (15). The far most common cause to secondary LLL in developed countries is cancer treatment such as surgery with lymph node dissection and radiotherapy (16-21).

In recent years, the terms primary and secondary lymphedema have been questioned due to evidence that there is a preexisting inherited lymphatic weakness in persons with cancer related lymphedema (22). Instead of the term secondary lymphedema Peters et al (22) suggest the term "latent lymphedema" to point out the inherited critical balance between lymph production and lymph drainage which is disturbed by surgery with lymph node dissection and radiotherapy. The authors estimated the prevalence of "latent lymphedema" to be 5% to 20% within the general population (22). For those where the diagnosis currently is primary lymphedema due to that the swelling is developed without any obvious insult to the lymphatic system but an inborn weakness a more correct name should be "constitutional lymphedema" (22). However, regardless of whether the diagnosis is caused by an insult to the lymphatic system or a congenital defect, the pathologic feature of the condition is the same causing increased size of the affected limb or limbs due to oedema and subcutaneous adipose tissue because of slow or absent lymph flow (23). In this thesis the concepts primary and secondary LLL will be used.

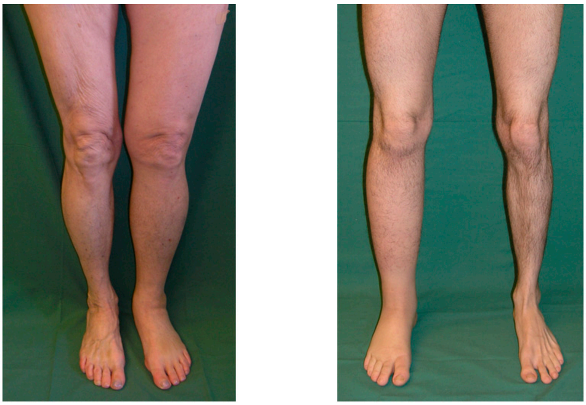

Figure 3. A woman with secondary cancer-related lower limb lymphedema in her left limb and a man with primary lower limb lymphedema in his right limb and foot. © Imke Wallenius

Risk factors

Studies have shown that major risk factors for LLL after treatment for cancer are surgery with extensive lymph node dissection and radiotherapy (16-21). After treatment for gynecological cancer some studies have also reported older age (16), and higher body mass index (BMI) (16, 17) to be risk factors, whereas other studies did not find radiotherapy (18), older age and higher BMI (24) to be risk factors. Some studies have also reported preoperative lymphedema (16), insufficient levels of physical activity (16) and cellulitis (17) as risk factors for LLL.

After treatment for malignant melanoma higher BMI (20) and peripheral vascular disease (19), have been reported as risk factors besides extensive lymph node dissection and radiotherapy, but in one of the studies higher BMI was reported not to be associated with a higher risk of LLL (19).

For those with primary LLL, cellulitis was reported to be a risk factor (25)

Diagnosis

It is well-known that the diagnosis of LLL is difficult due to that oedema of the lower limbs may have other causes such as venous insufficiency, post thrombotic swelling, capillary malformation, venous malformation, lipedema, obesity, posttraumatic swelling, or drug induced swelling (13). Also, systemic diseases such as cardiac, renal, hepatic, or rheumatologic diseases may cause oedema of the lower limbs (11). For the correct treatment it is of major importance to accurately determine if the cause of the oedema is lymphedema or not (25).

The function of the lymphatics can be investigated by imaging techniques where lymphoscintigraphy is the standard method (1, 26). This diagnostic imaging method uses a gamma camera to track radiotracers subcutaneously injected into the feet. The lymphatic vessels transporting the radiotracer will be visualized together with the drained lymph nodes in the lower limbs and pelvic region (11). In Sweden, lymphoscintigraphy is the preferred method when lasting oedema occurs without any known cause. Whilst for those with cancer related lymphedema with an onset within the first year after finishing surgical and/or oncological treatment the diagnosis is usually not complicated, but with a later onset, recurrence of the cancer should always be considered (27).

The diagnosis of cancer related lymphedema is based on history (i.e., surgery with lymph node dissection and/or radiotherapy) and a physical examination consisting of a combination of objective measurements and subjective assessments. In Sweden, two out of three criteria (see below) should be fulfilled for the diagnosis of lymphedema according to the national health care program for cancer rehabilitation 2023 (27):

1. Increased skinfold thickness in subcutis somewhere in the affected limb compared to the non-affected limb.
2. A volume increase (>5%) in the affected limb compared to the non-affected (28, 29) or to pre-surgery values. Determination of volume: the water displacement method or circumference measurements.
3. Increased local tissue water (ratio >1.2-1.45 based on upper limb lymphedema) (28) compared to non-affected limb or compared to pre-surgery measurement values measured by MoistureMeterD or LymphScanner.

A well-known aggravating factor concerning LLL is that the oedema may occur bilaterally in both primary LLL and in cancer related LLL (30). In those cases, a comparison between the limbs will not be useful because of an absence of a non-affected limb. To compare with pre-operative measurements are thus preferable (31) but in most clinics not achievable.

Incidence

There are several reviews, including some reviews using meta-analysis that report on the incidence of cancer related LLL (Table 1). The incidence rates vary considerably (from 0% to 56%) in those reporting LLL secondary to gynecological cancer treatment (17, 24). Apart from a difference in surgical intervention such as sentinel lymph node dissection or lymph node dissection, other explanations to the wide reported incidence rates are differences in length of follow-up, variation in adjuvant oncology treatment given, different measurement methods and thresholds used for the diagnosis of LLL. The authors in many of the incidence/prevalence studies highlight that there is an inconsistency in the diagnostic criteria for LLL used across studies and a lack of a uniform definition for LLL which aggravates the correct rates (17, 21, 24, 32, 33). Interestingly, Cormier et al (33) concluded that the likelihood of being identified with LLL almost doubled in studies where objective measurement methods were used compared to those with only subjective assessments.

The incidence of primary LLL is approximated to 1.15 in 100.000 persons with an onset early in life (15).

Table 1. Incidence/prevalence rates of cancer related lower limb lymphedema for different cancer diagnosis, cancer treatment and methods for detecting the diagnosis reported by prospective studies (PS), systematic reviews (SR) and meta-analysis (MA).

Authors, year	Cancer diagnosis	Treatment Surgery and RT	Incidence/ prevalence rates	Method/ methods for LLL diagnosis
Biglia et al., 2017, SR	Endometrial	Surgery and radiation varied	0-56%	Not specified, objective, subjective
Lindqvist et al., 2017, SR	Endometrial	Surgery and radiation varied	0-50%	Not specified, objective, subjective
Hayes et al., 2017, PS	Gynecological cancer	Surgery and radiation varied	25-39%	Objective (BIS) and self-reported
Huang et al., 2017, SR and MA	Vulvar cancer	Surgery SLND or LND	29%	Clinical diagnosis, objective, subjective
Cormier et al., 2010, SR and MA	Melanoma	Inguinofemoral LND	18%	Objective and subjective
Hyngstrom et al., 2013, PS	Melanoma	Inguinofemoral LND	27%	Objective (Perometer)
Söderman et al., 2016, SR and MA	Melanoma	Inguinal or ilioinguinal LND	33%	Not specified
Clinckaert et al., 2022, SR	Prostate	PLND + radiation	18-29%	Not specified and subjective
Cormier et al., 2010, SR and MA	Penile cancer	PLND	21%	Objective and subjective
Cormier et al. 2010, SR and MA	Bladder cancer	PLND	16%	Subjective
BIS, bioimpedance spectroscopy; LLL, lower limb lymphedema; LND, lymph node dissection; MA, meta-analysis; PLND, pelvic lymph node dissection; PS, prospective studies; RT, radiation therapy; SLND, sentinel lymph node dissection; SR, systematic review.				

Management of lower limb lymphedema

Measurements

To regularly perform measurements is important to be able to diagnose a condition, plan an appropriate treatment, and to evaluate short term or long-term effects of an intervention. In the management of LLL, a combination of objective measurements assessing the size of the swelling, the condition of the skin, movement/ function and psychosocial morbidity is recommended (13). The size of the lymphedema is determined by assessing volume. The three most common methods for measuring volume are the water displacement method using Archimede's principle, the Perometer which is an optoelectric device and the tape measurement method using circumferential measurements (CMs) for volume. The water displacement method is considered gold standard for upper limb lymphedema but is not common for LLL because of the bulky equipment needed and the large amount of water.

The Perometer uses infrared light to measure volume (34). The method is assumed to be very accurate (35) but the equipment is very expensive and not moveable, therefore not commonly used in clinical practice.

The tape measurement method is the most used method due to the simple equipment needed and CMs every 4th cm along the limb is considered reference standard for volume (31). But this method has been reported to be prone to error (36) due to the many manual steps and the knowledge about reliability of CMs for volume is limited (37). A disadvantage of this method is that the measurement procedure is time consuming. Only few studies have evaluated if fewer CMs than every 4th cm in persons with LLL can be used (38, 39), but these studies have limitations such as small sample sizes (38) and only few statistical analyses performed (39). More studies are therefore needed.

In the clinic, the difference between the limbs is often used to evaluate LLL status but in persons with a bilateral involvement a comparison between the limbs will not always be useful as there is no unaffected limb to compare with. Consequently, measurement methods not relying on comparison between the limbs are of interest. The tissue dielectric constant (TDC) method uses high-frequency electromagnetic waves to measure local tissue water in the skin. The MoistureMeterD is a handheld device for TDC measurements, it is handy and presents a measurement value within a couple of seconds. This method has been used for early diagnosis of upper limb lymphedema (40) and to evaluate the effects of compression treatment in upper limb lymphedema (41), in breast oedema (42) and in LLL (43). However, no studies have evaluated the test-retest reliability of TDC for local tissue water in healthy persons or in persons with LLL.

Another measurement method to assess LLL is the Bioimpedance spectroscopy (BIS). This method assesses the presence of excess lymph in the affected limb relative to that of the unaffected by measuring the electrical resistance (impedance) through the body at different frequencies (44, 45). This method has predominantly been evaluated for early diagnosis of unilateral and bilateral upper limb lymphedema and LLL (46) and is more frequently used in Australia and the USA. There is very limited knowledge about the test-retest reliability of impedance ratio of extracellular fluid (ECF) in persons with LLL (46) and the method is not widely used to evaluate effects of an intervention in persons with stable LLL.

Patient reported outcome measures are also important to use in the management of LLL. Generic outcome measures and disease specific outcome measures assessing quality of life, symptom intensity and distress, physical disabilities and psychosocial impairments associated with the LLL may improve the individual treatment by identifying the patient's perceived disability. The Lymphedema Quality of Life Inventory (LyQLI) is a disease specific quality of life questionnaire with items divided into: physical, psychosocial, and practical domains (47). The questionnaire has been developed and evaluated in Sweden in a population with various forms of lymphedema (48). The Lymphedema Functioning, Disability and Health Questionnaire for LLL (Lymph-ICF-LL) is a disease specific questionnaire including items in the following domains: physical function, mental function, general tasks/ household activities, mobility, and life domains/ social life (49). The questionnaire is based on the terminology of the ICF and has been developed and evaluated in a Dutch population (49). The questionnaire has been translated into Swedish (50).

Reliability of measurements

For repeated measurements in clinical practice or in research it is important to consider reliability and measurement errors (3). Reliability can be determined from measurements in the same subjects on two occasions, so called test-retest reliability. For a method to be clinically useful the measurements need to be stable, rendering small measurement errors. In a comprehensive reliability analysis, several statistical methods are required such as agreement between measurements, systematic changes in the mean and measurement errors (3). In lymphedema management repeated measurements on different occasions are common and therefore it is of great importance to determine if a change in lymphedema measurements is due to a treatment effect or an inherent variation. Overall, few studies have evaluated the test-retest reliability of CMs, TDC and impedance ratio in persons with LLL (5).

Assessing consequences of lower limb lymphedema

Consequences persons with LLL may experience in everyday life, work ability, leisure time activities and participation in social life (9, 48, 51-55) have had increased focus the last decade and especially the last five years. To measure and assess those consequences in a broader perspective is important to fully address the patient´s need of rehabilitation. To use the International Classification of Functioning, Disability and Health (ICF) framework, impairments, activity limitations and participation restrictions as well as environmental and personal factors will be addressed (56) (Figure 4). This bio-psycho-social model will provide a more holistic view of a person with a disease or disability (57). In Figure 4, common consequences of LLL in previous research (9, 48, 51-55) are sorted by the different components in the ICF.

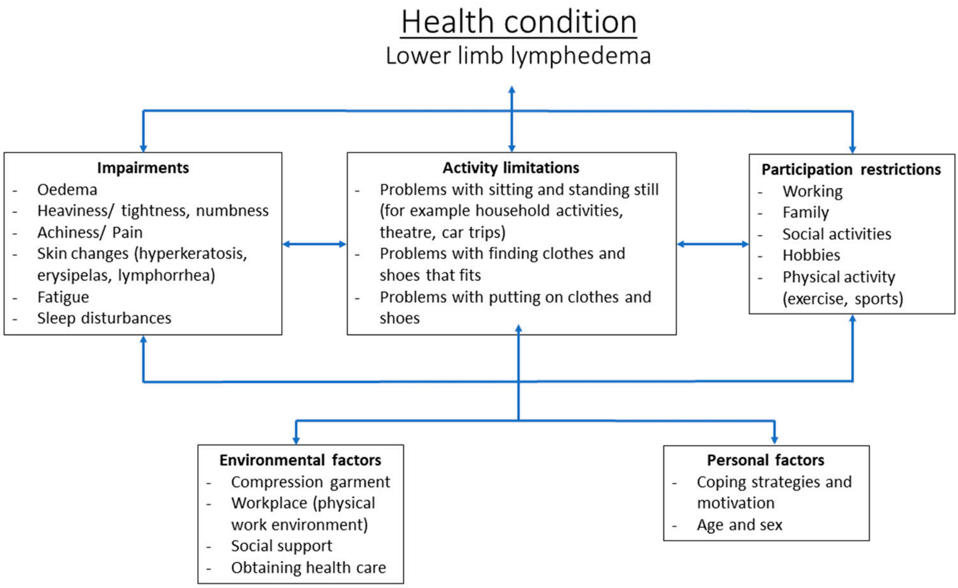

Figure 4. Consequences of lower limb lymphedema using the international Classification of Functioning, Disability and Health (ICF) model.

To what extent impairments, activity limitations and participation restrictions will affect patients varies. By using the ICF as a framework when evaluating consequences following LLL, planning treatment, evaluating short-term or long-term effects of an intervention, the healthcare providers will be aided to assess the patient´s function and disability in different areas, which will facilitate a more structured and holistic view of the patient´s health condition and needs (57).

To structure the rehabilitation by using a generic rehabilitation process consisting of four steps: assessment, goal setting, intervention, and evaluation (Figure 5) (58) may be helpful for the clinician as well as the patient. Focusing on lymphedema treatment and on different aspects of perceived disabilities caused by lymphedema will more clearly broaden the rehabilitation. By using this model in lymphedema clinics, together with both objective and patient reported outcomes a more structured way for rehabilitation may be facilitated. In lymphedema rehabilitation clinics the generic rehabilitation process in combination with the ICF framework is not widely used.

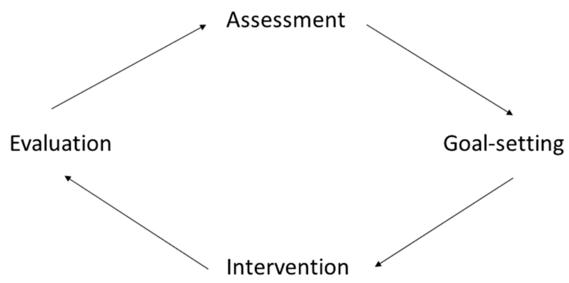

Figure 5. Generic rehabilitation process consisting of assessment, plan or goal setting, intervention and evaluation.

Treatment

Early diagnosis and treatment to keep the swelling as limited as possible is the primary focus in lymphedema treatment (27). The conservative treatment is performed by health care providers specialized in lymphedema treatment, so called lymphedema therapists. Traditionally, the treatment was given as a concept named the Complete Decongestive Therapy, CDT (59) consisting of skin care, manual lymphatic drainage, compression, and remedial exercise (13). During the last decade a more individualized treatment concept has been developed where compression garments and education in self-care are the main focus (Figure 6) (60). The length of the follow-up period is normally individualized based on a person´s need and the severity of the LLL. After some time, adjustment of the compression garments or repeated intensive treatment may be necessary. When there is comorbidity affecting the lymphedema or the ability to perform self-care, other health care providers may be involved in the treatment besides the lymphedema therapists (13). When the onset of LLL is early in life longer follow-up periods may be needed since adjustments of the compression garments are required continuously during growing up.

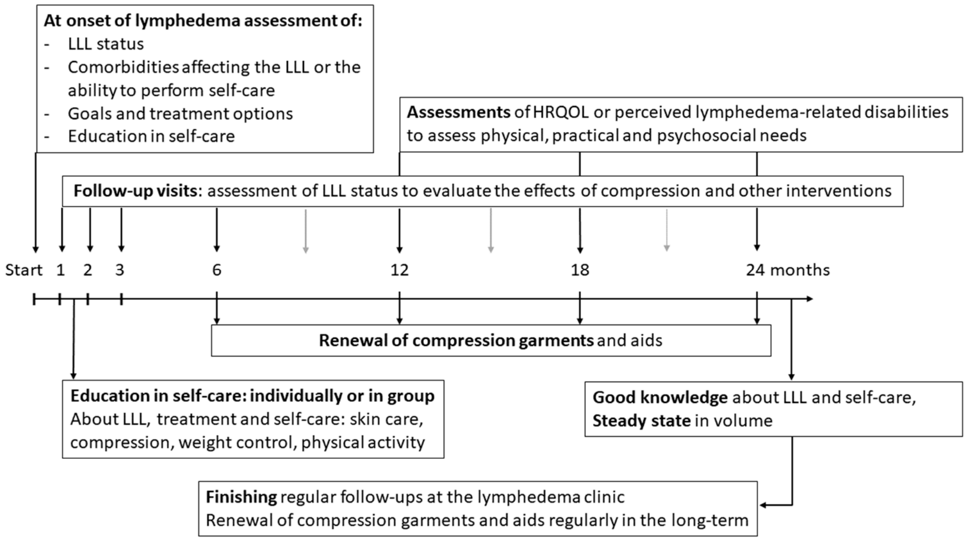

Figure 6. Example of a rehabilitation process in persons with LLL.

Exercise

Historically, exercise as part of the self-care in lymphedema management has been focused on daily performed remedial movements to support the lymphatic system and venous flow without increasing blood flow. During the last decades there has been increasing knowledge about the importance of exercise in cancer rehabilitation to improve cancer survival (61-64) and cancer treatment related symptoms(65). Another aspect is the general health benefits given by moderate exercise also for persons treated for cancer (66). Recently, a systematic review with meta-analysis concluded that aerobic and resistance exercise as well as unsupervised exercise guided by symptom response can be promoted for those with cancer-related lymphedema without worsening of the lymphedema (6). But only two of the studies included persons with LLL so even though the exercise recommendations for persons treated for cancer is convincing the knowledge about the effects on persons with LLL is limited.

Moderate intensity exercise has been evaluated in some studies including persons with LLL (67-69) but due to limitations such as small sample sizes (67, 68) and a mix of decongestive treatments plus exercise in the intervention group (69) additional RCTs are motivated.

WHO has recently updated their recommendations on physical activity in adults, older adults, and adults with a chronic condition (70). Their recommendations are weekly aerobic physical activity of at least 150 to 300 minutes at moderate-intensity or 75 to 150 minutes at vigorous-intensity or an equivalent combination. Regular twice a week muscle-strengthening activity is also included in these recommendations to achieve health outcomes such as improved all-cause mortality, cardiovascular disease mortality, incident hypertension, incident-specific cancers, incident typ-2 diabetes, mental health (reduced symptoms of anxiety and depression), cognitive health, sleep, and improved measures of adiposity (70). These general recommendations are important to consider for health care providers when giving advice about aerobic physical activity to persons with LLL. More knowledge about the efficacy and feasibility of moderate intensity exercise is therefore needed in persons with LLL.

Rationale for this thesis

Reliable measurements are needed to be able to diagnose a condition, plan for an appropriate treatment and to evaluate short-term or long-term effects of an intervention. In LLL management, CMs is often used for limb volume. To assess whether a change in measurements should be interpreted as a clinically relevant change or not, is important. When planning the studies in this thesis there was very limited knowledge about the reliability of CMs for volume in persons with LLL and if this measurement method could detect clinically relevant changes. Moreover, there is an increasing interest in measurement methods assessing LLL in other ways than with CMs, but the knowledge about the reliability of these methods and how sensitive they are to detect clinically relevant changes were lacking.

CMs every 4^{th} cm along the lower limb is considered reference standard for volume but is time consuming. Therefore, increased knowledge about whether fewer CMs could be used without decreasing measurement accuracy was needed.

Furthermore, in LLL management regular moderate intensity exercise is important to encourage because of the positive impact on cancer survival and the many health benefits of regular moderate exercise. However, at time of planning this thesis the knowledge about the effects of moderate intensity exercise on LLL was limited and based on previous beliefs that intensive exercise may worsen LLL. With this background an overall aim and specific aims were formulated.

Aims

Overall aim

The overall aim of this thesis was to increase knowledge about appropriate measurement methods to assess lymphedema in persons with primary or secondary lower limb lymphedema (LLL), to evaluate the test-retest reliability of those measurement methods and the benefit and feasibility of moderate intensive bicycling exercise.

Specific aims

- To evaluate test-retest reliability of circumferential measurements and tissue dielectric constant measurements in healthy women and men, and to define limits that indicate changes over time for a group of subjects and for single subjects.
- To evaluate the test-retest (intra-rater) reliability of impedance ratio for extracellular fluid, circumferential measurements for volume, and TDC for local tissue water in people with unilateral or bilateral LLL and measurement errors both for a group of persons and for a single individual.
- To establish the agreement between lower limb volume derived from circumferential measurements every 4^{th} cm (V4, reference standard), 8^{th} cm (V8), and 12^{th} cm (V12), and to evaluate the intra-rater test-retest reliability for each of the three measurement methods in persons with LLL.
- To investigate (1) the efficacy of bicycling exercise at a moderate intensity compared to usual daily activity, and (2) the feasibility of the bicycling exercise in LLL.

Methods

Study designs

This thesis is based on four studies where the study designs were cross sectional (Study I-III) and a pilot randomized controlled trial (pilot RCT, study IV). An overview of the study designs, participants, data collection and analyses are shown in Table 2.

Table 2. Overview of the methodology in the four included studies.

<table>
<tr><th>Study</th><th>I</th><th>II</th><th>III</th><th>IV</th></tr>
<tr><td>Study design</td><td>Cross-sectional</td><td>Cross-sectional</td><td>Cross-sectional</td><td>Pilot randomized controlled trial</td></tr>
<tr><td>Participants</td><td>N=61 (33 women) with no limb swelling.
Mean age (women) 52 years (SD 13).
Mean age (men) 52 years (SD 18).</td><td colspan="2">N=42 person (30 women)
Mean age 61 years (SD 14).
Duration of LLL mean 130 months (SD 92).</td><td>N=27 randomized to bicycling exercise n=16 (11 women) or control n=11 (6 women).
Median age 63 years (Q1: 54, Q3:73)
Duration of LLL median 9 years (Q1: 4, Q3: 18)</td></tr>
<tr><td>Data collection</td><td>Circumferential measurements (CMs) every 4th cm and tissue dielectric constant (TDC) measurements at 14 points at baseline and two weeks later.</td><td>CMs every 4th cm, impedance ratios and TDC measurements at 14 points at baseline and two weeks later.</td><td>CMs every 4th cm, every 8th cm, and every 12th cm at baseline and two weeks later.</td><td>CMs every 4th cm, TDC at 14 points and ECF R(0). Assessments of physical fitness, health-related quality of life and lymphedema-related disability were performed at baseline and postintervention.</td></tr>
<tr><td rowspan="4">Data analysis</td><td>Demographics, a study specific questionnaire</td><td colspan="3">Demographics and clinical characteristics from medical records and a study specific questionnaire</td></tr>
<tr><td colspan="2">Mean (SD, range)</td><td>Mean, (SD)
$ICC_{3.1}$</td><td>Median, interquartile range (Q1, Q3)</td></tr>
<tr><td colspan="3">Intraclass Correlation Coefficients ($ICC_{2.1}$), mean differences, 95% CI for mean differences, standard error of measurement (SEM, SEM%), smallest real difference (SRD, SRD%)</td><td rowspan="2">Descriptive statistics, Mann-Whitney U test and Wilcoxon signed rank test.</td></tr>
<tr><td></td><td colspan="2">Bland-Altman graph and 95% limits of agreement</td></tr>
</table>

Participants

In study I, the participants were recruited between September 2015 and Mars 2017. Information about the study was given orally and by written information to the employees at Skåne University Hospital, Lund, Department of Hematology, Oncology and Radiation Physics, by advertising in a local Facebook group and through family and friends to gain a sufficiently large number of participants. Inclusion criteria were 18 years or older and no current lower limb injury. Exclusion criteria were previous lower limb swelling, use of compression stockings to prevent swelling, previous orthopedic surgery or other intercurrent diseases such as circulatory or kidney failure symptoms, or muscular dysfunction in the lower limbs. A spread in age and a sample size close to 30 for each sex were sought among the volunteers. A total of 63 persons (33 women and 30 men) volunteered for the study, 38 of them were employees, 20 were recruited from the local Facebook group, 5 were family and friends. Thirty-three women and 28 men completed the study. The mean age for the women was 52 years (SD 13; range 25-77) and for the men 52 years (SD 18; range 24-76) respectively, their mean BMI was 26 (SD 4; range 20-37) and 26 (SD 4; range 22-41) respectively.

In study II and III, the participants were recruited between April 2018 and Mars 2019. Potential participants were identified through medical records and by colleagues at the Lymphedema unit, Skåne University Hospital (Figure 7).

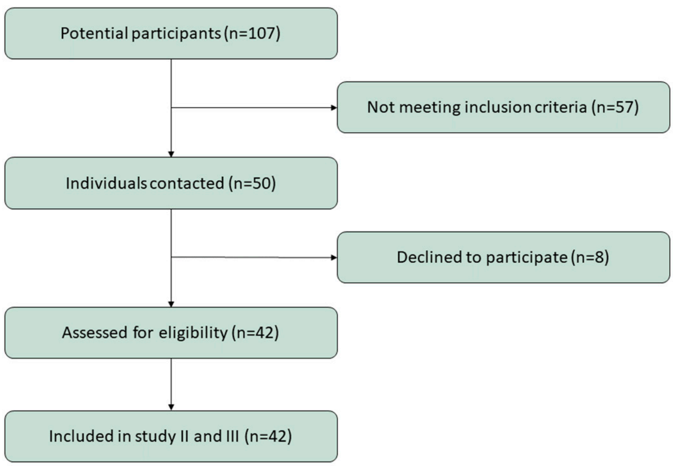

Figure 7. Flowchart of recruitment process to study II and III

Inclusion criteria were: 18 years or older, a diagnosis of unilateral or bilateral, primary or secondary LLL (assessed by lymphoscintigraphy and/or a medical specialist), persistent lymphedema for the last 6 months (a stable volume of the lower limbs for the last 6 months i.e., a total volume variation <5% for each limb), treatment with compression stockings during the day or during day and night according to usual care. The exclusion criteria were ongoing treatment to reduce the limb volume; comorbidity such as heart failure, kidney disease or venous insufficiency that could affect swelling of the lower limbs; prosthetic knee or hip implants; intake of diuretic medication or any other drug that may interfere with the volume of the lower limbs; inability to understand written or oral information. A sample size close to 30 for each sex were sought among the participants. One hundred and seven were identified as potential participants and 57 of these did not meet inclusion criteria (not stable lower limb volume, comorbidity affecting the volume or prosthetic implants in knee or hip) (Figure 7). Written information about the study was sent to 50 potential participants. After 1-2 two weeks they were contacted by phone (by CJ) for further information and asked if they were willing to participate in the study. Forty-two persons were willing to participate and were assessed for eligibility. For inclusion, thickness of the subcutaneous tissue as a sign of lymphedema (71) had to be present. If the compression garments were older than 2 months at time of inclusion new ones were ordered and used for two weeks before the first test occasion.

Thirty women and 12 men were included in study II and III. Their mean age were 61 years (SD 14), and their mean BMI was 27 (SD 5). Thirty of them had secondary LLL, mainly due to gynecological cancer treatment (n=17). The duration of the LLL varied from 1 year to 40 years among the participants and 24 of them had unilateral LLL. Characteristics of the participants are presented in Table 3.

Table 3. Characteristics for the participants in study II and III

Variables	
Gender: women/ men, n (%)	30 (71)/ 12 (29)
Age: years, mean (SD)	61 (14)
BMI: kg/m^2, mean (SD)	27 (5)
Diagnosis, n	
Gynecological cancer	17
Melanoma	5
Urological cancer	4
Other	4
Primary lymphedema	12
Duration of lymphedema; months, mean (SD)	130 (92)
Lymphedema; bilateral/ unilateral, n (%)	18 (43)/ 24 (57)

In study IV (the pilot RCT), the participants were recruited between November 2018 and November 2022. The recruitment was stopped from Mars 2020 to Mars 2022 due to the COVID-19 pandemic. Potential participants were identified through medical records and by colleagues at the Lymphedema unit, Skåne University

Hospital and at two regional Hospital outpatient rehabilitation clinics in the southern health care region of Sweden (Central Hospital of Kristianstad and Ystad Hospital). Inclusion and exclusion criteria were the same as in study II and III. Written information about the study was sent to 71 potential participants of which 29 previously had participated in study II and III (Figure 8). After 1-2 weeks they were contacted by phone (by CJ) for further information and asked if they were willing to participate in the study.

Thirty-tree persons were willing to participate and were assessed for eligibility. For inclusion, thickness of the subcutaneous tissue as a sign of lymphedema (71) had to be present. If the compression garments were older than 2 months at time of inclusion new ones were ordered and used for two weeks before the first test occasion. A total of 33 persons were included in the study and 27 fulfilled the study.

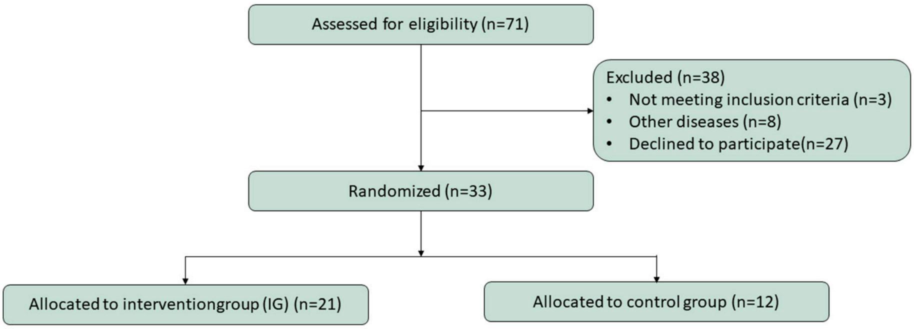

Figure 8. Flowchart of the recruitment process in study IV

Their median (Q1, Q3) age was 63 (54,73) years and their median BMI (Q1, Q3) was 26 (23, 30). Twenty of them had secondary LLL, mainly due to gynecological cancer treatment (n=12). The duration of the LLL varied from 1 year to 39 years among the participants and 20 of them had unilateral LLL. During the last 6 months, 11 participants reported hardly any to easy weekly physical activity, whereas 16 participants reported moderate to high weekly physical activity. Demographics and characteristics of the participants are presented in Table 4.

Table 4. Demographics and characteristics of the participants in the intervention group and the control group (study IV).

Variables	Intervention group (n=16)	Control group (n=11)
Gender: women/ men, n	11/ 5	6/ 5
Age: median (Q1, Q3)	60 (54, 71)	71 (58, 75)
BMI: kg/ m^2, median (Q1, Q3)	27.4 (24.3, 31.3)	24.8 (20.5, 26.4)
Physical activity, exercise and housework*, n		
Hardly any to easy physical activity	5	6
Moderate to high physical activity	11	5
Working/ retired, n	9/ 7	5/ 6
Diagnosis, n		
Gynecological cancer	10	2
Melanoma	2	2
Urological cancer	1	3
Other	0	1
Primary lymphedema	3	3
Duration of lymphedema: years, median (Q1, Q3)	11 (6, 17)	7 (3,18)
Lymphedema: bilateral/ unilateral, n	5/ 11	2/ 9

*Physical activity/ exercise level weekly the last 6 months according to the six-point scale by Frändin&Grimby,1994.

Data collection and outcomes

Before all the assessments, demographics and characteristics such as age, gender, body weight and body height were collected in all studies. In study II-IV additional information such as leisure time physical activity status during the last 6 months by the Frändin & Grimby physical activity scale (72), working status (active or sedentary job, or retired), diagnosis of the cancer if cancer-related LLL, primary or secondary LLL, duration of lymphedema, bilateral or unilateral affected, and experience of heaviness and/ or tightness in the limb affected by the LLL during the last week were collected. Manual examination to assess presence of increased subcutaneous thickness was performed.

The three measurement methods used for LLL status were: CMs for volume, TDC for local tissue water and impedance for ECF. (Thresholds for each of these measurement methods were used to describe the participants in study II-IV, shown in appendix.)

In study I, the assessments were performed at the Lymphedema unit, Skåne University Hospital and for those recruited from the Facebook advertisement the assessments were performed in a separate room at a hair salon in a village outside Lund. Having a separate room to conduct the measurements located close to the participants was assumed to be attractive. The measurements were performed during the morning at about the same time. Prior to each test occasion the participants were asked to maintain a similar activity schedule in the morning. The test procedure was as follows: 10 minutes of rest in a supine position with the legs uncrossed, then the measurement on the right limb followed by the left limb. For TDC measurements, the participants turned over to prone lying. To standardize the measurement procedure first CMs by the tape measurement method were taken followed by TDC for local tissue water by the MoistureMeterD.

In study II and III, the assessments were performed at the Lymphedema unit, Skåne University Hospital. The measurements were performed during the morning at about the same time. Prior to each test occasion the participants were asked to maintain a similar activity schedule in the morning. The same standardized procedure as in study I was used. To standardize the measurement procedure first measurements of impedance ratios for extracellular fluid (ECF) by the Bioimpedance spectroscopy were taken, followed by CMs and then TDC.

In study IV, the assessments were performed at the Lymphedema unit, Skåne University Hospital, for the participants recruited at the Central Hospital of Kristianstad and at the Ystad Hospital, the assessments were performed in separate rooms at each hospital. At baseline, all the assessments were performed by CJ and after the intervention a physiotherapist (AJ) blinded to participant group status, performed all the assessments in Lund except for CMs and markings for TDC which was performed by CJ.

The measurements were performed during the morning at about the same time. The test procedure started with the two questionnaires: the Lymphedema Quality of Life Inventory (LyQLI) and the Lymphoedema functioning, disability, and health questionnaire (Lymph-ICF-LL). Then the participants rested in a supine position for 10 minutes. The same standardized measurement procedure as in study II was conducted for the LLL status and lastly physical fitness by a submaximal cycle ergometer test. For the efficacy of the intervention, both primary and secondary outcomes measures were assessed. The **primary outcomes** were lower limb volume, local tissue water and ECF which were obtained with CMs, TDC and ECF R(0), respectively. The **secondary outcomes** were physical fitness, health related quality of life and lymphedema related disability which were obtained with a submaximal cycle ergometer test, the LyQLI and the Lymph-ICF-LL, respectively. **Feasibility** was assessed by information collected from the logbooks: date of each exercise session, total duration at each session, mean heart rate for each session and CMs every two weeks for volume and control of the logbook.

An overview of the measurements used in study I-IV is shown in Table 5.

Table 5. Overview of the measurements used in study I-IV

	Variable	Method measure	Study I	Study II	Study III	Study IV
LLL status	Volume	Circumferential measurements (CMs)	x	x	x	x
	Local tissue water	Tissue dielectric constant (TDC)	x	x		x
	Impedance of extracellular fluid (ECF)	Arm-leg impedance ratio or ECF R(0) value		x		x
	Presence of thickness of the subcutaneous tissue (or not)	Palpation of skin and subcutaneous tissue		x	x	x
Physical fitness	VO2max	Submaximal cycle ergometer test				x
Disease specific HRQOL	Perceived HRQOL the last 4 weeks	Lymphedema Quality of Life Inventory (LyQLI)				x
Impairments in function, activity limitations, and participation restrictions	Perceived lymphedema- related disability the last 2 weeks	Lymphoedema functioning, disability, and health questionnaire (Lymph-ICF-LL)				x
Sensory function	Perceived heaviness and/ or tightness in the affected limb or limbs	Visual analogue scale (VAS)		x	x	x
Leisure time physical activity	Perceived physical activity level the last 6 months	The Frändin & Grimby physical activity six- point scale.		x	x	x

Measurements

Lower limb volume

The tape measurement method was used to assess volume by CMs every 4th cm (73). To calculate volume a standard spread sheet program with the formula for a truncated cone $V=\frac{\pi}{3}h(r_1^2 + r_2^2 + r_1 \cdot r_2)$ was used (31) (study I-IV). The measurement method consisted of a 110-cm measuring board, a 20-cm ruler, a water-soluble pen, and a narrow retractable measuring tape. The foot and heel were placed against the footplate of the measuring board, markings were made on the lateral side of the limb and identified with the short end of the ruler on the measuring board at each distance starting 10 cm above the heel (Figure 9) and ending near the groin. CMs to the nearest millimetre were taken once at each marking by placing the measuring tape close to the skin. The repeatability standard deviations (SDs) of this method have been estimated to be 95 mL (CI 78-112 in healthy persons) (37).

For participants with bilateral LLL, the limb with the larger volume was referred to as the more affected limb and the limb with the smaller volume was referred to as the less affected limb. For participants with unilateral LLL, the affected limb was referred to as the more affected limb and the non-affected limb was referred to as the less affected limb.

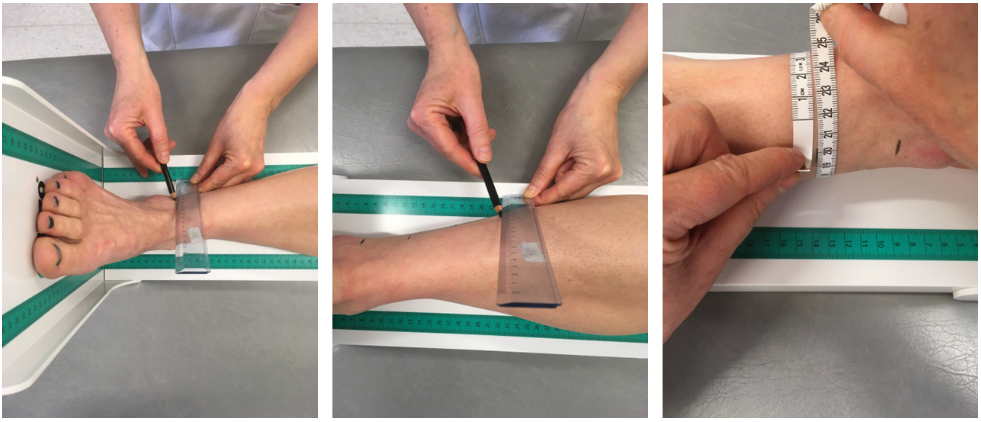

Figure 9. Marking the starting point 10 cm above the heel and then every 4th cm along the limb. Circumferential measurements to the nearest millimetre (to the right). © Karin Johansson

Local tissue water

The MoistureMeterD with a M25 probe was used to assess local tissue water by TDC (Delfin Technologies Ltd. Finland) (study I, II and IV). The device transmits a high frequency electromagnetic (EM) wave of 300 MHz into an open-ended coaxial probe in contact with the skin. Most of the EM energy is absorbed by the tissue water, while the remainder is reflected to the coaxial line and an electrical parameter, the TDC, directly proportional to tissue water content of the skin can be calculated (74). The M25 probe has an effective depth of 2.5 mm which represents the depth where the EM field has attenuated to 37% of the value at the skin surface. The TDC scale ranges from 1 to 78 based on the percentage of fluid at the measurement site where a TDC value of 1 represents no water and a TDC value of 78 represents 100% water. To cover the limb a total of 14 points distributed on four levels: distal calf, mid-calf, distal thigh, and proximal thigh (Figure 10) were identified and marked using of a 110-cm measuring board, a 20 cm ruler, a tape measure, and a water-soluble pen.

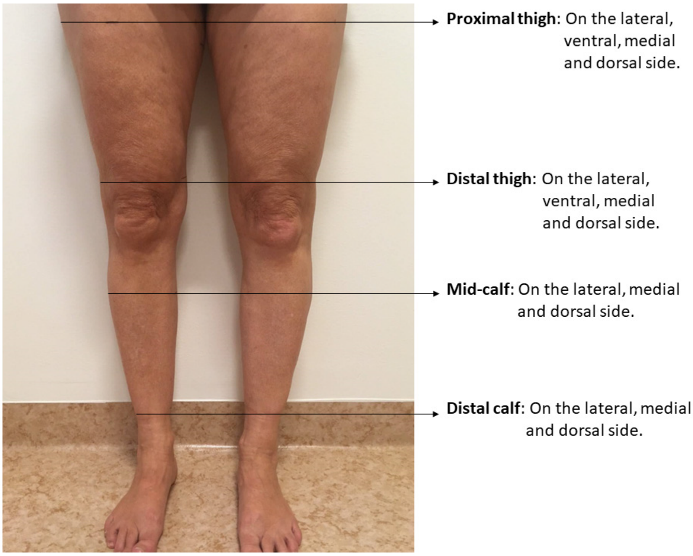

Figure 10. Four levels of were the 14 measuring points of TDC measurements were located. © Lotta Jönsson.

A standardized protocol to identify the points were developed and described in study I (paper I, Table 1). This protocol was used in study I, II and IV. TDC measurements were taken (Figure 11) in triplicated at each point (75) and the average of the two closest values were used in the analysis.

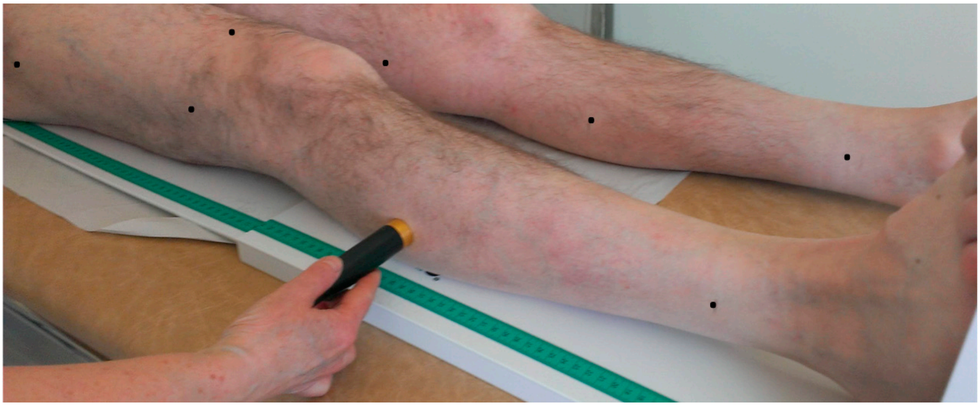

Figure 11. Measurements of tissue dielectric constant (TDC) on the mid-calf level. © Charlotta Jönsson

Impedance of extracellular fluid (ECF)

The Bioimpedance spectroscopy (SEAC SFB7 monitor, Impedimed, Brisbande, Queensland, Australia) was used to assess impedance of ECF by arm-leg ratio (study II) or ECF R(0) (study IV). The BIS technique uses a tetrapolar electrode arrangement with two measurement electrodes positioned one at each end of the segment to be measured and two drive electrodes each positioned distal to the measurement electrodes. A low-level current is passed between the two drive electrodes and the measurement electrodes record the segment's impedance (R) (45). The resistance, that corresponds to ECF (R0) and to total body fluid (Rinf), was determined, and intracellular fluid (Ri) was calculated (45).

The electrode positions for the impedance assessments followed the recommendations for the upper limbs: on the dorsal side of the wrists at the level of the process of the radial and ulnar bones (45) and for the lower limbs: on the dorsal side of the foot midway of the malleoli (76). The drive electrode sites were 5 cm distal to the above-described positions, namely, on the dorsal side of the third metacarpal bone and the third metatarsal bone, respectively (45) (Figure 12). Before application of the gelled electrodes, the skin was cleaned with an alcohol wipe. Each segment was measured once on each test occasion and the resistances corresponding to ECF R(0) were noted. In study II, the arm-to-leg impedance ratio was calculated for each person, using the formula: dominant arm R0/dominant leg R0 and non-dominant arm R0/ non-dominant leg R0, respectively (46). Side of dominance was defined by the dominant arm. In study IV, the R(0) value was used.

Figure 12. Impedance of extracellular fluid was assessed by bioimpedance spectroscopy (BIS).
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Physical fitness

A submaximal bicycle ergometer test (77) was used to assess physical fitness and an estimation of maximal oxygen uptake (VO2max) was evaluated from heart rate and workload (study IV). Heart rate and cadence were monitored every minute as was the person's perceived exertion using the Borg RPE-scale (78). The cadence was 50 revolutions per minute until "steady state" was reached. For health safety reasons the test was interrupted if the heart rate exceeded 150 beats per minute (77). The coefficient of variation for this test is 9.8% (79) meaning that this changes of VO2max for a group of persons should be interpreted as a real clinical change.

Disease specific HRQOL

The Lymphedema Quality of Life Inventory (LyQLI) (47) was used to assess perceived HRQOL (study IV). This disease specific questionnaire comprises 45 items in three domains: physical, psychosocial, and practical. The impact of lymphedema is scored on a 4-point Likert scale ranging from 0 to 3, where higher scores indicate a more negative impact. The LyQLI has shown good validity, reliability (47) and responsiveness (80) and a Swedish version was used.

Lymphedema-related disability

The Lymphedema functioning, disability, and health questionnaire for LLL (Lymph-ICF-LL) (49) was used to assess impairments, activity limitations and participation restrictions by perceived lymphedema-related disability (study IV). The questionnaire is based on the ICF (the International Classification of Functioning, Disability and Health) (81) and comprises 28 items in 5 domains: physical function, mental function, general tasks/ household activities, mobility activities and life domains/ social life. The impact of LLL is scored on a 100-millimeter VAS where a higher score indicates a more negative impact. The questionnaire has shown good validity and reliability (49) and a Swedish version was used (50).

Heaviness and/ or tightness in the lymphedema limb or limbs

The Visual Analogue Scale (VAS) (82) was used to assess perception of heaviness and/ or tightness in the limb or limbs affected by the lymphedema over the past week. Ratings on the 100-mm VAS with the endpoints "no discomfort" and "worst imaginable discomfort" was used as clinical characteristics (study II-IV). In study IV, the VAS was also used before and after each exercise session to assess perception of heaviness and/ or tightness in the lymphedema limb or limbs. This information was part of the logbook data. This scale has previously been used in persons with upper limb lymphedema (83, 84).

Leisure time physical activity

The Frändin & Grimby physical activity six-point scale (72) was used to assess leisure time physical activity during the last 6 months and used as clinical characteristics (study II-IV). The six-point scale ranging from hardly any physical activity (level 1) to high or very high regular aerobic physical activity several times a week (level 6). In study II and III, the ratings from 1 to 6 were used. In study IV, the ratings were dichotomized to "hardly any to easy PA" (level 1-3) and "moderate to high PA" (level 4-6).

Thickness of subcutaneous tissue

Presence of increased subcutaneous tissue on the lower legs and/ or thighs was assessed during manual examination (study II-IV). The participants were in a supine position with knee bent. Palpation was performed by pinching subcutaneous tissue in the calf and thigh using the thumb and index finger (Figure 13). This test has shown high sensitivity and moderate specificity to detect dermal backflow (disturbance of the superficial lymphatic system) according to the lymphoflouroscopic images in persons with upper limb lymphedema (71). Increased skin thickness has also shown a strong correlation with the degree of swelling and duration of lymphedema in persons with chronic upper limb lymphedema (85). For all participants in study II-IV, presence of increased subcutaneous tissue in the lower limbs was a sign of verifying residual swelling.

Figure 13. Palpation of thickness of the subcutaneous tissue on the lower legs and thighs. © Charlotta Jönsson

Reliability of measurements

To assess the intra-rater test-retest reliability of continuous measurements (study I-III), the measurements are to be conducted by the same rater on two occasions, often separated by hours or days. Several statistical analyses are recommended to be used such as the agreement between measurements, systematic changes in the mean and measurement errors (3, 4). When assessing the test-retest reliability of measurements the sample size is also of importance to consider and we followed the recommendations stating that around 30 participants are required to form clinically useful measurement errors for a group of persons and in a single person (86).

Analysis of agreement between measurements

In the analysis of agreement between measurements, the relationship between two sets (or more) of repeated measurements are evaluated using the intraclass correlation coefficient (ICC) for continuous variables. If the measurement values for each person on the two test occasions are identical the ICC is 1 (4). There are different ICCs available for different study designs, and generally the values of the different ICCs are often very similar (3). For intra-rater test-retest reliability, the $ICC_{2.1}$ is recommended (4). The ICC values in study I, II and III were interpreted according to Fleiss (87), where values below 0.40 represent poor reliability, values between 0.40 and 0.75 represent fair to good reliability, and values above 0.75 represent excellent reliability. According to Lexell & Downham (3) the ICC has several advantages e.g., can be used with small sample sizes and with data from more than two test occasion. The ICC can sometimes give misleading results because the analysis is highly sensitive to the spread of the measurements between subjects. Therefore, additional analyses are needed (3).

Assessment of systematic changes in the mean

Normally there is a variation in mean values (mean difference, $\bar{d}$) between two test occasions and this variation can be caused by a random change or a systematic change. A random change may be caused by the variability in the equipment, in the method used or inherent biological variability, i.e., the variability in the actual test situation. A systematic change is a non-random change caused by the performance by the participants i.e., a learning effect or fatigue (3). If zero is included in the 95% CI for the mean change, no systematic changes in the mean are present (88). In case of systematic changes in the mean, it must be analysed and remedied before proceeding with further analysis (4). Another way to visually evaluate changes in the mean is by the so-called Bland-Altman graph. Here, the differences in the mean between the two test occasions (test occasion 2 minus test occasion 1) are plotting against the mean for each participant, together with the 95% limits of agreement (LOA) (3, 88) (study II). The Bland-Altman graphs were also used in study III to visually illustrate the variability between the methods.

Assessment of measurement errors

The assessments of measurement errors consist of the measurement variability where the size of the variability between the measurements is quantified. The smaller the variability, the easier to detect a variation. The standard error of measurement (SEM) and the smallest real difference (SRD) were used in study I-III to assess measurement errors. The SEM gives the limit for the smallest change that indicate a real change for a group of persons (3) and is defined as SEM=SD(1-ICC)$^{0.5}$ (4). For a group of persons, this value is often referred to as the "within-subject variation", "typical error" or "typical variation" (86). The SEM gives the measurement variability in absolute values.

The SRD represents the limit for the smallest change that indicates a real change for a single person and is defined as follows (3): SRD=1.96 x SEM x $\sqrt{2}$. The relative value of the SEM (SEM%) and SRD (SRD%) were used in the analyses since a relative value is independent of the units of measurements and thus more easily interpreted (3). The relative value of SEM was calculated as follows: SEM%= (SEM/mean) x 100 (3) and the relative value of SRD was calculated as follows: SRD%=(SRD/mean) x 100 (89). An acceptable measurement variability for a group of persons (SEM%) is considered to be less than 10% and for a single person (SRD%) is considered to be less than 30% (89).

Agreement between measurement methods

In study III, CMs every 4th cm from study II was used for the V4 method, every 8th cm for the V8 method and every 12th cm for the V12 method. To define total limb volume based on the V8 method and the V12 method the formula for a truncated cone was rewritten. To ensure that the same limb length measurements were used for all methods, the length for the V4 method was used as a preference. The most proximal volume segment was therefore converted to either a 4 cm segment or an 8 cm segment for the V8 method or the V12 method (Table 6).

Table 6. Total length of the lower limbs and number of measuring points for circumferential measurements every 4th cm (V4), every 8th cm (V8) and every 12th cm (V12).

Total length of the lower limb measured in cm	**V4 method,** number of measuring points	**V8 method,** number of measuring points	**V12 method,** number of measuring points
70	16	9*	6
74	17	9	7*
78	18	10*	7**
82	19	10	7

*Of which a 4 cm segment as the top cone; **Of which an 8 cm segment as the top cone.

Efficacy of bicycle exercise versus usual daily activity

In study IV, the measurements were performed at baseline (test occasion 1, T1) and after the 8-week intervention (test occasion 2, T2). For participants randomized to intervention group there were also visits every two weeks during the intervention (Figure 14).

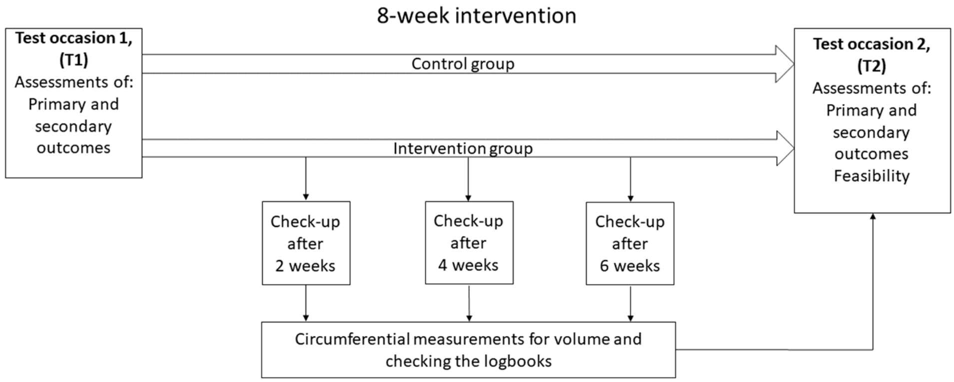

Figure 14. Timeline for the assessments in pilot RCT (study IV).

Randomization

Randomization to intervention group (IG n=21) or control group (GC n=12) was done with an allocation ratio of 2:1. This ratio was chosen due to the limited number of suitable participants and the assumption that a higher opportunity to be randomized to exercise would attract participants to enrol. The random allocation sequence was done using a computer software program administered by one of the authors (KJ). The participants were told not to discuss their group assignment with the blinded assessor at T2. For those randomized to CG the same instructions to perform the cycle exercise after the trial was offered.

Description of bicycling exercise at moderate intensity

The exercise in the IG consisted of bicycling 3 to 5 times a week, with a mean intensity of 40-59% of the Heart Rate Reserve (HRR). HRR was calculated as followed: (estimated maximum heart rate minus resting heart rate) x (%HRR) plus resting heart rate. The exercise was home-based and conducted on an indoor spinning bike provided by the research team or on a private bicycle, or at a gym. A heart rate monitor (Polar FS1) was provided to check the correct intensity during the session, the total time of exercise, and the mean heart rate (information for the logbook). Each session started with a 5-minute warm-up (cycling at self-chosen pace), then the monitor was switched on to check the correct intensity, and bicycling was continued at a moderate intensity for 30-60 minutes. Thereafter the monitor was switched off, followed by cooling down for 5 minutes (biking at a self-chosen pace) then stretching. Verbal and written information about the monitor, recommended cadency of 60-90 revolutions/ min, stretching and how to complete the logbook at each exercise session was given on the first test occasion.

Description of usual daily activity

The exercise in the CG consisted of habitual daily physical activity routines or exercise, during the 8-weeks. After the trial, the participants in the CG were offered the same instructions and a heart rate monitor to perform the cycling exercise.

Feasibility of the bicycling exercise

Feasibility was assessed by retention, adherence, and adverse events. Before and after each exercise session a logbook was completed with:

- Ratings of experienced heaviness and/ or tightness in the lymphedema limb/ limbs on a VAS.
- Total time for the exercise registered by the heart rate monitor.
- Average heart rate registered by the monitor.
- Perceived exertion on the Borg RPE-scale, recommended was 12-14 ("somewhat hard").
- Any adverse event or personal reflection related to the exercise.

Retention was assessed by withdrawal rate and adherence was assessed by data from the logbook, achieving the prescribed dose of exercise by fulfilling at least 3 sessions per week, for 30 to 60 minutes and within moderate intensity. At T2, the participants also answered a question about whether this exercise was new to them, replaced other kind of exercise or added to existing exercise. Visits every two weeks were performed for CMs (Figure 14) because an increased volume of more than 5% was considered to be an adverse event. In case of an increased volume, discontinuation of the intervention and the commencement of intensive decongestive treatment. During these visits the logbook was also checked with the purpose to facilitate continued participation.

Statistical analyses

In study I-IV, descriptive statistics were used for the participants' demographic and clinical characteristics as well as other appropriate variables by calculating frequencies, means and standard deviations or medians, minimums and maximums, quartiles (Q1 and Q3) or ranges with minimums and maximums (Table 7). All analyses were performed using IBM SPSS Statistics version 24 and 29 (IBM, Armonk, New York, USA).

Table 7. Overview of the statistical methods used in paper I-IV

	Paper I	Paper II	Paper III	Paper IV
Descriptive statistics				
Mean±SD	x	x	x	
Median (Q1, Q3)				x
Number (n)		x	x	x
Proportion (%)		x	x	x
Ranges (min-max)		x	x	
Statistical analyses				
Intraclass correlation coefficient ($ICC_{2.1}$)	x	x	x	
Intraclass correlation coefficient ($ICC_{3.1}$)			x	
Change in the mean	x	x	x	
Standard error of measurement (SEM, SEM%)	x	x	x	
Smallest real difference (SRD, SRD%)	x	x	x	
Bland-Altman graphs (95% limits of agreement)		x	x	
Mann-Whitney U test				x
Wilcoxon signed rank test				x

In study I-III, the test-retest reliability analyses were performed with the $ICC_{2.1}$, the changes in the mean, SEM/ SEM% and SRD/ SRD%. In study II, the differences between measurements were visually quantified with the Bland-Altman graphs including the 95% LOA.

In study III, the agreement between the methods was analysed by $ICC_{3.1}$. To visually quantify the difference between the V4 and V8 methods and the V4 and V12 methods, the Bland-Altman graphs were used including the 95% LOA. The test-retest analyses were made with the $ICC_{2.1}$, the changes in the mean, the SEM/ SEM% and the SRD/ SRD%.

In study IV, non-parametric tests were used for the analyses because the data was not normally distributed. A sum score for the outcomes of the LyQLI and for the outcomes of Lymph-ICF-LL were used in the analyses. Mann-Whitney U test was used for evaluating differences between the groups at T1 and for evaluating differences in changes (T1-T2) between the groups. Wilcoxon signed rank test was used for evaluating changes between T1 and T2 within each group. A p-value of <0.05 was considered statistically significant.

Ethical considerations

All studies were approved by the regional ethical committee review board in Lund Sweden, Dnr 2016/136. Amendments were approved for study I, II and III, Dnr 2017/228 and for study IV, Dnr 2020/05960. All studies were conducted in accordance with the Declaration of Helsinki. Study IV was registered in ISRCTN10242104.

In study I, all participants received written and oral information about the study when being informed by CJ or KJ. At this first contact some of the participants accepted to participate and time for inclusion were planned while others wanted some time to consider. These potential participants were contacted after one or two weeks and were given further information about the study, the aim, and processes.

In study II-IV all participants received written information about the study and were contacted by phone after one or two weeks by CJ. Additional oral information about the study, the study's processes and goals were given, and the participants rights to discontinue further participation whenever they wanted to during the study without this affecting their contact with the rehabilitation unit. For those who accepted to participate this information was repeated at the first test occasion before given written informed consent.

The measurement methods used in study II-IV were new to most of the participants except for CMs. Information about TDC measurements, arm-leg ratio and ECF R(0) were therefore given in conjunction with the measurements being carried out. In study IV, the questionnaires concerning health-related quality of life and perceived lymphedema-related disability are not routinely used in the clinic and were new to most of the participants. Some of the questions may trigger feelings of sadness, but also feelings of recognition and that the questionnaire addresses key concepts about what it is like to have lymphedema. A sensitivity to these feelings and suggestions on how these feelings could be taken care of further were given by CJ.

Results

Reliability of measurements

Lower limb volume

Test-retest reliability data of CMs (study I-III) are presented in Table 8. On average, in study I there were 15 days (SD 3) between the two test occasions for women and 16 days (SD 2) for men. In study II and III there were on average 14 days (SD 2) between the two test occasions. In all three studies, the ICCs were 0.99. The mean differences were small (ranged from -8 ml to 88 ml) and a systematic difference in the mean was found in the left limb in healthy men, indicating a higher value on the second test occasion. In all three studies, the SEM% ranged from 1.1% to 1.4% and the SRD% ranged from 3.1% to 3.8% (Table 8).

Table 8. Test-retest reliability of circumferential measurements (volume) in study I-III

Volume		$ICC_{2.1}$	$\bar{d}$ (T2-T1)	95% CI for $\bar{d}$	SEM%	SRD%
Study I						
Women	Right limb	0.99	3	-46 to 52	1.1	3.1
	Left limb	0.99	0	-58 to 57	1.3	3.6
Men	Right limb	0.99	49	-11 to 110	1.2	3.4
	Left limb	0.99	88	28 to 148	1.3	3.6
Study II						
Participants with LLL	MA limb	0.99	3	-51 to 56	1.3	3.6
	LA limb	0.99	21	-26 to 69	1.2	3.4
Study III						
V4 method	MA limb	0.99	3	-51 to 56	1.3	3.6
	LA limb	0.99	21	-26 to 69	1.2	3.4
V8 method	MA limb	0.99	-8	-62 to 47	1.3	3.5
	LA limb	0.99	21	-31 to 72	1.4	3.8
V12 method	MA limb	0.99	7	-51 to 64	1.4	3.8
	LA limb	0.99	26	-27 to 79	1.3	3.7

ICC, intraclass correlation coefficient; $\bar{d}$, mean difference; CI, confidence interval; MA, more affected; LA, less affected; SEM%, relative value of the standard error of measurement; SRD%, relative value of the smallest real difference. V4, circumferential measurements every 4th cm; V8, circumferential measurements every 8th cm; V12, circumferential measurements every 12th cm.

Local tissue water and impedance in ECF

In study I, test-retest reliability of TDC at 14 points in the right and left limb in both women and men are presented in Table 9. The ICCs in women ranged from 0.63 to 0.93, and in men from 0.21 to 0.89. There was a systematic change in the mean in many of the measuring points in women but mostly in one of the limbs, implying higher values on the second test occasion. In men, a systematic change in the mean was seen only in two measuring points. The SEM% ranged from 4% to 10% in women, and from 4% to 15% in men. The SRD% ranged from 11% to 28% in women and from 11% to 40% in men.

Table 9. Test-retest reliability of TDC measurements in 14 measuring points in healthy women and men (study I).

Study I	Limb	$ICC_{2.1}$		$\bar{d}$ (T2-T1)		95% CI for $\bar{d}$		SEM%		SRD%	
		W	M	W	M	W	M	W	M	W	M
TDC											
Distal calf											
Lateral	Right	0.77	0.43	1.5	1.8	-0.3 to 3.2	-0.1 to 3.7	10	8	27	23
	Left	0.80	0.27	2.8	1.5	1.1 to 4.5	-1.0 to 4.0	10	11	28	30
Medial	Right	0.64	0.71	0.8	1.3	-0.4 to 2.0	-0.4 to 2.9	8	9	23	25
	Left	0.66	0.78	1.2	0.4	0.0 to 2.4	-0.9 to 1.7	9	7	24	19
Dorsal	Right	0.63	0.21	2.3	1.1	0.8 to 3.9	-1.7 to 3.8	10	13	28	37
	Left	0.93	0.35	0.4	-2.4	-0.5 to 1.3	-5.2 to 0.4	5	15	14	40
Mid-calf											
Lateral	Right	0.84	0.76	0.5	0.2	-0.2 to 1.3	-1.3 to 1.7	5	8	14	21
	Left	0.77	0.74	0.8	-0.6	-0.1 to 1.7	-1.8 to 0.5	6	6	18	17
Medial	Right	0.73	0.85	0.9	0.4	0.1 to 1.8	-0.9 to 1.7	7	7	18	20
	Left	0.82	0.84	0.6	0.9	-0.2 to 1.5	-0.3 to 2.0	6	7	16	18
Dorsal	Right	0.78	0.81	1.2	0.9	0.3 to 2.0	0.0 to 1.7	7	5	18	15
	Left	0.84	0.76	1.2	0.9	0.5 to 1.9	0.1 to 1.8	6	5	16	15
Distal thigh											
Lateral	Right	0.67	0.58	0.4	0.1	-0.5 to 1.3	-2.0 to 2.2	7	12	20	33
	Left	0.81	0.82	0.8	0.2	0.0 to 1.5	-1.0 to 1.4	6	7	16	19
Ventral	Right	0.69	0.59	0.7	0.3	-0.3 to 1.7	-1.1 to 1.6	6	7	17	20
	Left	0.80	0.65	0.9	0.9	0.1 to 1.6	-0.2 to 2.0	5	7	14	18
Medial	Right	0.77	0.72	0.9	0.1	0.0 to 1.7	-1.0 to 1.2	7	7	19	19
	Left	0.84	0.66	0.8	-0.1	0.2 to 1.4	-1.0 to 0.9	5	6	14	17
Dorsal	Right	0.83	0.80	0.1	0.5	-0.5 to 0.7	0.0 to 1.2	5	4	13	12
	Left	0.82	0.74	0.0	0.4	-0.7 to 0.6	-0.5 to 1.3	5	6	13	16
Proximal thigh											
Lateral	Right	0.69	0.83	0.6	0	-0.2 to 1.4	-1.2 to 1.2	6	6	17	18
	Left	0.68	0.82	1.0	0	0.2 to 1.8	-0.9 to 1.3	6	6	18	17
Ventral	Right	0.77	0.89	0.4	0.3	-0.3 to 1.1	-0.5 to 1.0	5	5	14	12
	Left	0.84	0.89	0.7	0.5	0.2 to 1.1	-0.2 to 1.1	4	4	11	11
Medial	Right	0.78	0.42	0.3	0.1	-0.4 to 1.0	-1.2 to 1.5	5	8	14	23
	Left	0.81	0.63	0.8	0.5	0.2 to 1.5	-0.3 to 1.3	5	5	14	15
Dorsal	Right	0.66	0.82	0.8	0.8	-0.1 to 1.6	-0.1 to 1.6	5	5	15	13
	Left	0.74	0.77	0.5	1.2	-0.2 to 1.3	0.3 to 2.1	5	5	13	15

ICC, intraclass correlation coefficient; $\bar{d}$, mean differences; M, men; SEM%, relative value of the standard error of measurement; SRD%, relative value of the smallest real difference; TDC, tissue dielectric constant; W, women

In study II, the test-retest reliability of arm-leg impedance ratio and TDC measurements in the more affected and less affected limb are presented in Table 10. For the impedance ratio, the ICCs ranged from 0.79 to 0.90. The mean differences ranged from 0.02 to 0.03 and in the more affected limb there was a systematic difference in the mean because zero was not included in the 95% CI. The SEM% was 5% for both limbs and the SRD% was 14%. For the TDC, the ICCs ranged from 0.68

to 0.96 in the more affected and less affected limb, respectively. The mean differences ranged from -0.8 to 0.9 and no systematic difference was present in any of the measurements. The SEM% ranged from 4% to 9% and the SRD% ranged from 12% to 27% in the more affected and less affected limb, respectively.

Table 10. Test-retest reliability of arm-leg impedance ratio and TDC measurements in 14 points in the more affected and less affected limb of 42 persons with lower limb lymphedema (study II).

Study II	Limb	$ICC_{2.1}$	$\bar{d}$ (T2-T1)	95% CI for $\bar{d}$	SEM%	SRD%
Arm-leg impedance ratio						
Arm-leg ratio	MA limb	0.90	0.03	0.003 to 0.065	5	14
	LA limb	0.79	0.02	-0.014 to 0.049	5	14
TDC						
Distal calf						
Lateral	MA limb	0.84	0.4	-0.9 to 1.6	7	19
	LA limb	0.78	0.3	-1.3 to 1.9	9	24
Medial	MA limb	0.86	-0.1	-1.3 to 1.4	8	22
	LA limb	0.71	0.1	-1.2 to 1.4	8	22
Dorsal	MA limb	0.79	1.3	-0.2 to 2.7	9	24
	LA limb	0.76	1.3	-0.2 to 2.9	10	27
Mid-calf						
Lateral	Ma limb	0.88	-0.6	-1.7 to 0.6	8	21
	LA limb	0.92	0.2	-0.5 to 1.0	5	13
Medial	MA limb	0.96	0.1	-0.7 to 0.8	4	12
	LA limb	0.87	-0.2	-1.2 to 0.7	6	18
Dorsal	MA limb	0.87	-0.2	-1.1 to 0.7	6	16
	LA limb	0.95	0.3	-0.4 to 0.9	4	12
Distal thigh						
Lateral	MA limb	0.84	0.4	-0.9 to 1.8	9	25
	LA limb	0.77	0.2	-0.8 to 1.3	8	23
Ventral	MA limb	0.71	0.1	-1.0 to1.1	6	17
	LA limb	0.68	-0.3	-1.3 to 0.6	7	18
Medial	MA limb	0.89	-0.5	-1.6 to 0.7	8	23
	LA limb	0.90	0.2	-0.6 to 0.9	5	15
Dorsal	MA limb	0.91	-0.5	-1.5 to 0.6	7	21
	LA limb	0.86	-0.8	-1.6 to 0.0	7	19
Proximal thigh						
Lateral	MA limb	0.94	-0.3	-1.3 to 0.6	6	17
	LA limb	0.85	0.0	-0.8 to 0.9	6	17
Ventral	MA limb	0.95	0.1	-0.8 to 0.9	5	15
	LA limb	0.89	0.3	-0.5 to 1.1	6	17
Medial	MA limb	0.93	0.9	-0.2 to 2.0	6	17
	LA limb	0.79	0.7	-0.3 to 1.8	7	21
Dorsal	MA limb	0.83	0.4	-0.4 to 1.2	6	15
	LA limb	0.79	0.5	-0.2 to 1.2	6	14

ICC, intraclass correlation coefficient; $\bar{d}$, mean difference; CI, confidence interval; MA, more affected; LA, less affected; SEM%, relative value of the standard error of measurement; SRD%, relative value of the smallest real difference; TDC, tissue dielectric constant.

The Bland-Altman graphs

In study II, the Bland-Altman graphs were used to illustrate the differences between the test occasions plotted against the mean of the two test occasions for the arm-leg impedance ratio, CMs and TDC in 4 points in the more affected limb (paper II, Figure 2). The graphs reveal that the differences between the two test occasions were small for all three methods. For the impedance ratio, generally higher values on the second test occasion, also shown by the 95% CI for the mean differences which did not include zero (Table 10).

Agreement between measurement methods

In study III, the agreement between the V4 and V8 methods and between the V4 and V12 methods were high, shown by the high $ICC_{3.1}$ (ICC 0.999 and ICC 0.998, respectively). The mean differences were small for the V4 and V8 methods (ranged from -31 to -28 ml; 95% CI -43 to -13) and for the V4 and V12 methods (ranged from -52 to -35 ml; 95% CI -61 to -9) in the more affected and less affected limb, respectively. (Table 11).

Table 11. Agreement between the V4 and V8 methods and between the V4 and V12 methods in the more affected and less affected limb, respectively, in 42 persons with lower limb lymphedema.

	$ICC_{3.1}$	95% CI for ICC	$\bar{d}$	95% CI of $\bar{d}$	95% LOA
V4 and V8 methods					
MA limb	0.999	0.998 to 1.000	-31	-43 to -18	-110 to 49
LA limb	0.999	0.998 to 1.000	-28	-42 to -13	-117 to 62
V4 and V12 methods					
MA limb	0.998	0.996 to 0.999	-35	-61 to -9	-198 to 129
LA limb	0.998	0.994 to 0.999	-52	-81 to -23	-236 to 132

CI, confidence interval; $\bar{d}$,mean difference; ICC, intraclass correlation coefficient; LOA, limits of agreement; MA, more affected; LA, less affected

The Bland-Altman graphs revealed the small variability between the V4 and V8 methods and between the V4 and V12 methods (Figure 15). No systematic relationship between the differences were revealed in the graphs or no increase in variability for larger volumes. The 95% LOA ranged between -117 ml to 62 ml for the V4 and V8 methods and between -236 ml to 132 ml for the V4 and V12 methods (Table 11). The slightly wider 95% LOA for the V4 and V12 methods compared to the V4 and V8 methods is also well illustrated in the Bland-Altman graphs (Figure 15).

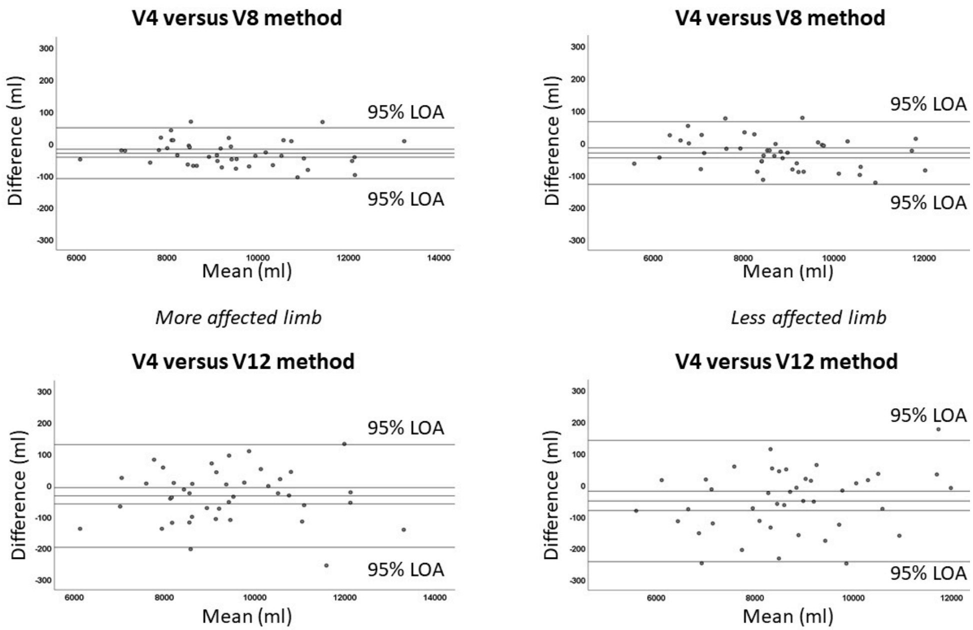

Figure 15. Bland-Altman graphs where the differences between the V4 and V8 methods and between the V4 and V12 methods is plotted against the mean of the methods, for each limb separately.

In study III, test-retest reliability analyses were also performed for the three methods. This analysis showed high reliability (ICCs 0.99) for all three methods, low mean differences (ranged from -8 ml to 26 ml) and no systematic differences in the mean for any of the three methods. The SEM% ranged from 1.2% to 1.4% and the SRD% ranged from 3.4% to 3.8% in both limbs, implying that all three methods are reliable presenting small measurement errors (Table 8).

Efficacy of bicycling exercise versus usual daily activity

Baseline characteristics of the primary and secondary outcomes in the IG and CG are presented in Table 12, separated for the more affected limb and less affected limb. At baseline, there was a significant difference between the groups for the volume which was larger in both the more affected limb (p=0.008) and the less affected limb (p=0.03) in the IG compared to the CG. No other significant differences between the groups at baseline were found.

Table 12. Baseline measurements of the primary and secondary outcomes in the intervention group and control group in study IV.

Variables	Intervention group (n=16)	Control group (n=11)
Primary outcomes	Median (quartile Q1, Q3)	Median (quartile Q1, Q3)
Volume, ml		
MA limb	9574 (8582, 10518)	7926 (7210, 8695)
LA limb	8676 (7349, 9878)	7009 (6405, 7969)
Local tissue water, TDC (high)		
MA limb	42.5 (39.6, 48.9)	39.0 (35.9, 48.3)
LA limb	32.4 (28.5, 41.7)	32.8 (29.3, 39.8)
ECF R(0)*		
MA limb	286.1 (214.8, 565.3)	285.4 (253.5, 319.3)
LA limb	308.8 (256.6, 568.0)	315.7 (263.5, 368.3)
Secondary outcomes		
Physical fitness, VO2 max	2.7 (1.8, 3.1)	2.4 (1.8, 2.8)
HRQOL, LyQLI, sum score	0.7 (0.2, 1.1)	0.3 (0.1, 0.6)
Lymphedema related disability, Lymph-ICF-LL, sum score	14.6 (6.1, 27.1)	6.4 (2.7, 13.4)
MA, more affected; LA, less affected; TDC, tissue dielectric constant, the point with the highest value at T1 comparing to values in healthy persons (study I); ECF, extracellular fluid; VO2max, maximal oxygen consumption; LyQLI, Lymphedema Quality of Life Inventory; ICF, International Classification of Functioning, Disability and Health; LL, lower limbs. Impedance R(0)*, n=24.		

Between group differences

Regarding changes in primary outcomes (T1-T2), no significant differences between the groups were found after the intervention. Regarding changes in secondary outcomes (T1-T2), a significant difference between the groups were found in lymphedema-related disability after the intervention, in favour of the IG (-1.1, p=0.05). No other significant differences in changes between the groups in any of the secondary outcomes were found (Table 13).

Within group differences

Regarding primary outcomes, in the IG a significant decrease in TDC in the point with the highest value and in ECF R(0) was found after the 8-week intervention in the more affected limb. The median difference for TDC was -2.2 (p=.013) and for ECF R(0) -13.2 (p=.004), respectively. Regarding secondary outcomes, significant improvements in the IG were found for physical fitness, health-related quality of life and lymphedema-related disability. The median differences for V02max were +0.5 L/min (p=.019), for the LyQLI -0.1 points (p=.049) and for the Lymph-ICF-LL -2.4 points (p=.029), respectively. For the CG no significant median differences were found from T1 to T2 in neither primary nor secondary outcomes (Table 13).

Table 13. Differences in changes in primary and secondary outcomes within the groups (WG) and between the groups (BG) after the 8-week bicycle exercise intervention.

	Intervention group (n=16)	p-value WG	Control group (n=11)	p-value WG	p-value BG
Primary outcomes					
Volume, ml					
MA limb	63 (-28, 178)	*n.s*	93 (-121, 221)	*n.s*	*n.s*
LA limb	69 (-60, 242)	*n.s*	46 (-45, 195)	*n.s*	*n.s*
TDC (high)					
MA limb	-2.2 (-5.8, -0.2)	**0.013**	-0.4 (-3.8, 1.0)	*n.s*	*n.s*
LA limb	-1.2 (-3.1, 0.3)	*n.s*	0.1 (-1.6, 1.1)	*n.s*	*n.s*
Impedance of ECF R(0)					
MA limb	-13.2 (-147.1, -3.8)	**0.004**	-11.9 (-16.6, 11.4)	*n.s*	*n.s*
LA limb	-10.0 (-24.8, 17.9)	*n.s*	-19.1 (-35.6, 25.7)	*n.s*	*n.s*
Secondary outcomes					
VO2 max	0.5 (0, 0.7)	**0.019**	0.2 (-0.2, 0.4)	*n.s*	*n.s*
LyQLI, sum score	-0.1 (-0.2, 0.0)	**0.049**	0.1 (-0.1, 0.1)	*n.s*	*n.s*
Lymph-ICF-LL, sum score	-2.4 (-8.7, -0.4)	**0.029**	0.2 (-1.8, 4.7)	*n.s*	**0.050**
WG, within the groups; BG, between the groups; TDC, tissue dielectric constant compared to highest value compared to healthy women and men (study I); ECF, extracellular fluid; VO2 max, maximal oxygen consumption; LyQLI, Lymphedema Quality of Life Inventory; ICF, International Classification of Function, Disability and Health; LL, lower limb					

Feasibility of the bicycling exercise

All participants in the IG except one reached 24 sessions of cycling exercise during the intervention, approximated to three times per weeks during the 8-week intervention. Thirteen participants performed the exercise within the prescribed recommendation for frequency, intensity, and duration for most of the weeks and four of them even had a higher intensity in more than half of their sessions. Three participants fulfilled the recommendations for most of the weeks, but for some only twice weekly exercising or shorter sessions or at a lower intensity than prescribed. One adverse event in terms of a volume increase of >5% was found in one participant after 6 weeks. Further participation was discontinued, and intensive decongestive treatment was given.

Information from the logbooks showed that ratings of perceived heaviness and/ or tightness after each exercise session compared to before did not change or only minor changes were found. Ratings of perceived exertion using the Borg RPE-scale showed that most of the sessions were within the recommended range. A variety of personal reflections on the performed exercise were reported in the logbooks: transitory experience of cramping (n=2), a tingling sensation in the lymphedema limb or limbs (n=3), muscle soreness (n=3), increased self-confidence with exercise (n=5), a better feeling in the lymphedema limb after exercising (n=3) and a willingness to perform the exercise even though cycling also occurred in everyday life (n=8). Problems with the bicycle or heart rate monitor were also reported (n=2). Seven participants reported bicycling as a new exercise for them, while nine participants used the bicycling as a complement or a replacement for existing exercise.

Discussion

General discussion

The overall aim of this thesis was to increase knowledge about appropriate measurement methods to assess lymphedema in persons with primary or secondary LLL, to evaluate the test-retest reliability of those measurement methods and the efficacy and feasibility of moderate intensive bicycling exercise.

The test-retest reliability analysis was therefore applied in three of the studies in this thesis. In study I, the results showed that volume and local tissue water can be reliably measured in healthy persons. Consequently, CMs and TDC measurements may therefore facilitate the choice of objective measurements in the early diagnosis of persons at risk of cancer related LLL. The results also showed that volume, impedance of ECF and local tissue water can be reliably measured in persons with LLL. The measurement errors in these analyses were low or acceptable, which may contribute to a clinically usefulness of this value when evaluating the effects of treatment or other interventions in the clinic. Based on CMs every 4^{th} cm (reference standard), two other measurement methods were defined and evaluated. The results showed that the agreement between these methods were high and indicated that CMs every 8^{th} cm can be used instead of every 4^{th} cm without decreasing the reliability. The reduced time with CMs every 8^{th} cm will make this method less time demanding in the clinic.

During the last decades, knowledge about the importance of moderate physical activity in cancer rehabilitation to improve survival has increased. The general health benefits given by moderate aerobic exercise for persons with a chronic condition has highlighted the need for exercise interventions. The result in this pilot RCT showed that an 8-week home-based moderate bicycling intervention is feasible due to high adherence to the exercise protocol and has few adverse events. A significant between-group difference in perceived lymphedema-related disability in favour of the IG was found. Within the IG, significant decreased TDC and impedance of ECF were found after the intervention, as were significant improvements in physical fitness and in HRQOL. No changes were found in the CG. Consequently, moderate intensity bicycle exercise seems to be beneficial in persons with mild to moderate LLL without risking to worsening the LLL.

In this thesis, the ICF model was used to present consequences following LLL described as impairments, activity limitations and participation restrictions. Together with the generic rehabilitation process presented and an overview of a rehabilitation process in persons with LLL, the increased knowledge of reliable measurement methods can thus be put into a meaningful clinical and daily life context.

Reliability of measurements

Agreement between measurements

CMs every 4th cm for volume in healthy women and men (paper I) and in persons with mild to moderate LLL (paper II) showed excellent reliability according to Fleiss (87) (ICCs 0.99) (1986). Only a few studies have evaluated the test-retest reliability of CMs in the lower limbs (37, 90, 91). Our ICCs are somewhat higher than the ICCs presented by Bakar et al (91) (ICCs ranged from 0.65 to 0.99) where separate CMs on nine anatomical landmarks were used in the analyses. Sawan et al (37) and te Slaa et al. (90) did not present ICCs. Consequently, different statistical analyses were used in these studies and therefore comparison between the results are difficult. Volume of the lower limbs can also be determined with a perometer and our results for CMs are in line those presented by Tan et al (92) (ICC 0.99) conducting a test-retest analysis with repeated measurements taken at one test occasion. Our results are also in line with ICCs values presented in reliability studies evaluating CMs in persons with upper limb lymphedema (ICCs ranged from 0.96 to 0.99) (93-95)

Measurements of TDC in 14 points in lower limbs of healthy women and men (paper I) and in persons with mild to moderate LLL (paper II) showed fair to excellent reliability in healthy women (ICCs 0.63 to 0.93), poor to excellent reliability in men (ICCs 0.21 to 0.89) and fair to excellent reliability in persons with mild to moderate LLL (ICCs 0.68 to 0.96). Our results in healthy women and in persons with LLL are in line with ICCs presented by deVriese et al (96) for the unaffected limb (ICCs ranged from 0.77 to 0.95) and for the affected limb (ICCs ranged from 0.79 to 0.95) in persons with upper limb lymphedema.

Measurements of arm-leg impedance ratio in persons with mild to moderate LLL showed excellent reliability according to Fleiss (87) (ICCs 0.79 to 0.90) (paper II). The ICC presented by Czerniec et al. (93) evaluating reliability of upper limb measurements in women with upper limb lymphedema is somewhat higher (ICC 0.95) than in our study. The ICC has many advantages in the test-retest reliability analysis (3) but a disadvantage to consider is that the ICC can be low if the sample is homogeneous, and therefore a set of statistical analyses is recommended (3, 4).

Changes in the mean

The changes in the mean between the two test occasions were generally small and for most of the measurements no systematic differences were seen as zero was included in the 95% CI for the mean differences. However, in the TDC measurements in healthy women (paper I) there was a systematic difference in nine points in the left limb and in four points in the right limb consisting of higher values on the second test occasion. The reason for this is unknown, but if it was related to hormonal variation, a difference would more likely be seen in both limbs and not preferably in the left. If the difference would be due to limb dominance the changes in the means would be in both women and men, not preferably in women. However, a change in the mean is important both to consider and to be further investigated (3). In study I, a reasonable conclusion would be that the TDC values are reliable in healthy women because the mean differences for TDC were small, and the 95% CIs were narrow.

Measurement errors

For CMs, the SEM% ranged from 1.1% to 1.3% and the SRD% ranged from 3.1% to 3.6% in healthy persons (paper I). In persons with LLL, the SEM% ranged from 1.2% to 1.4% and the SRD% ranged from 3.4% to 3.8% (paper II and III). To compare our data with other studies is not straight forward because there are very few studies evaluating measurement errors using CMs. However, our SRD values from study I presented as absolute SRD (262-335 ml) are in line with a previous study by Sawan et al (37) (270 ml) using CMs every 4th cm in healthy persons. For persons with LLL, the SEM was 120 ml (paper III) in the more affected limb. Our SEM value is slightly higher than SEM values presented for upper limb lymphedema ranging from 63 ml of 94 ml (93, 95) but considering that the volume of the lower limbs is larger than the volume of the upper limbs our results are in line with theirs.

Measurement errors for TDC measurements were acceptable in healthy women and in most points in healthy men (SEM% ranged from 5% to 10% in women and from 4% to 13% in men; SRD% ranged from 11 % to 28% in women and from 11% to 40% in men) (paper I). In persons with mild to moderate LLL, the measurement errors were acceptable (SEM% ranged from 4% to 10%; SRD% ranged from 12% to 27%). The only study presenting measurement errors of local tissue water have evaluated points in persons with upper limb lymphedema using absolute values of SEM with the PWC method (percentage water content) (96). Our SEM values ranged from 1.1 to 5.2 (paper I) and from 1.4 to 3.6 in persons with LLL (paper II). The absolute SEM (PWC values) in the study by De Vrieze et al (96) ranged from 1.5 to 2.1 (non-affected limb), and from 2.1 to 4.1 (affected limb). Considering that absolute PWC values are higher (using a range between 1 to 100) than absolute TDC values (using a range between 1 and 78) the measurement errors in our studies seem to be in line with those presented by De Vrieze et al. (96).

Measurement errors for the impedance ratio were acceptable (SEM%: 5% and SRD%: 14%) and corresponded to an absolute SEM of 0.07 which is in line with the results of Czerniec et al (93) showing an absolute SEM of 0.06 in interlimb R0 ratio in upper limb lymphedema.

Measurement errors presented as SEM% and SRD% are valuable and useful in the clinic as they are easy to interpret. They represent the limits for normal variations of measurement values for a group of persons and for a single person, respectively. This means that a change in measurement values smaller than the SEM% or the SRD% after an intervention most likely is to be considered too small to be clinically relevant (3). Whereas a change outside the SEM% or the SRD% most likely is to be considered a clinically relevant change. Acceptable limit for SEM% is reported to be <10% and for SRD% <30% (89). In study II, the SRD% for CMs ranged from 3% to 4% which seems to be clinically useful. If the SRD% for CMs had turned out to be closer to 10% it would still be considered acceptable (89) but probably not clinically useful because 10% in volume is quite a lot. In a lower limb volume of 9000 ml, a change of 10% corresponds to 900 ml which may be considered a lot in the clinic. Whereas a change of 4% in the same limb corresponds to 360 ml which seems to be much more reasonable. Therefore, when using the SRD% (and SEM%) in the clinic the values need to be put in the context of where they are used and in some cases the SRD% seems to be too high whereas the SEM% is the more reasonable value to be used (3).

Agreement between measurement methods

The agreement between the V4 method, the V8 method, and the V12 method was high ($ICC_{3.1}$) (paper III). For the V4 and V8 methods the agreement was slightly higher than for the V4 and V12, shown by the narrower 95% LOA for the V4 and V8 methods than for the V4 and V12 (-117 ml to 62 ml and -236 ml to 132 ml, respectively). The test-retest reliability for the three measurement methods was high (ICCs ranged from 0.993 to 0.995) and the measurement errors low (SEM% ranged from 1.2% to 1.4% and SRD% ranged from 3.4% to 3.8%) (paper III). Our results from the agreement analyses shown by the 95% LOA are in line with Sukul et al (97) presenting a narrow 95% LOA (-123 ml to 33 ml) when evaluating the accuracy of volume based on the water displacement method, with the tape measurement method (using CMs every 3rd cm) in young men. Other studies where the agreement between methods for limb volume have been evaluated in lower limbs (92) and in upper limbs (98, 99) the 95% LOA in the analyses had been wider. The authors therefore concluded that the methods were not interchangeable. Based on the agreement analyses in study III and the test-retest reliability, the V8 method is recommended to be used instead of the V4 method for volume in persons with mild to moderate LLL with the purpose of saving time in clinical settings.

Efficacy of bicycling exercise versus usual daily activity

In this pilot RCT, a significant change between the groups after the intervention was found in perceived lymphedema-related disability in favour of the IG (paper IV). Within the IG, significant decrease in ECF R(0), improvements in TDC, V02max, and HRQOL were found. No changes were found in the CG. An important conclusion in this study based on these results is that moderate exercise can be performed without worsening LLL. This result is in line with results presented by Do et al (69) showing no worsening in LLL status after 4 weeks of moderate intensity exercise in combination with decongestive exercise. In their RCT significant improvements between the groups were found for physical function, fatigue, muscle strength in favour of the IG. These improvements were likely a consequence of the exercise even though it was performed for a limited time (only 4 weeks).

In this study, three different quantitative measurement methods were used to evaluate LLL status (primary outcomes). These three methods measure LLL in different ways, CMs for volume, TDC for local tissue water and impedance for ECF (R). In the within group analyses, we found significant decrease in TDC and in impedance of ECF (paper IV), there were no changes in CMs. The decrease in TDC were found in one measurement point with a high value at the T1. The reason we chose to evaluate this point was that a point with a high value will more probably change compared to a point with a low value. A possible explanation to the improvements in TDC could be that the intensive muscle activity combined with compression stockings may reduce local tissue water in a point with a high value. If local tissue water was moved to another location or absorbed by the lymphatic system is unclear and further research to evaluate changes in TDC measurements are recommended. There was a significant decrease in impedance of ECF R(0) in the IG. Our result is quite the opposite to the result presented by Dionne et al (68) where a significant decrease in ECF was found after a 6-week exercise intervention. Our result implies an increase in ECF, because the relationship between resistance and volume is inversely related. There was however no indication of a worsening of the LLL, based on CMs or TDC and we therefore suggest that a possible explanation to the changes in impedance measurements could be a change in the composite of the lower limb due to a slightly larger muscle mass caused by the exercise. Based on these results, we suggest follow-up visits with volume control at the start of moderate exercise.

CMs every 4^{th} cm for volume was used in study IV. According to the results in study III, we could have used CMs every 8^{th} cm for volume to save time, but since the inclusion in study IV started in 2018 and at a point where we did not have the results for paper III formulated, CMs every 4^{th} cm for volume was used throughout study IV.

In study IV, in the between group analysis there was a significant improvement in perceived lymphedema related disability in favour of the IG. In exercise studies including persons with LLL it is probably more common to find improvements in muscle strength, physical function, and fatigue (69), but improvements in health-related quality of life and in perceived lymphedema related disability may be as important as the physical improvements found after exercise for persons with LLL.

Bicycling exercise was chosen due to the assumption that regular repeated muscle activity may promote circulatory improvements in the lymphatic vessels by increasing the pumping capacity and thereby affecting the LLL in a positive way. Our study showed however no changes in volume in the IG. A decrease in volume has been shown in an exercise study where the participants with breast cancer related arm lymphedema performed moderate aerobic exercise for eight weeks with pole walking (84). But since these results have not been confirmed in other exercise studies including persons with lymphedema (6) the main goal for exercising will be the more general health benefit of moderate intensity exercise and to lower the risk of cancer recurrence (100) in those with cancer related LLL.

Feasibility of the bicycling exercise

The feasibility was investigated by retention, adherence, and adverse events. The retention rate (82%) was high, because only two participants stopped due to lack of time, whereas three were stopped due to the COVID pandemic. Thus, 27 participants fulfilled the intervention, of which 16 in the IG (paper IV). Adherence to the exercise protocol was 81%, since 13 participants fulfilled the prescribed intensity, frequency, and duration for most of their weeks. Similar results have been shown in a study by Johansson et al (101) where unsupervised water-based exercise was performed twice weekly for 8 weeks and in a study by Jönsson et al (84) where home-based pole walking where performed three to five times per week for 8 weeks. Some advantages of home-based exercise are that it is budget friendly, the environment is comfortable, no pressure from others and can be done whenever there is time. In our study the use of regular check-ups every two weeks for volume control and control of the logbooks were found to be supportive. The social support from family, friends and healthcare professionals have been identified as an important facilitator for physical activity (102). Also, to consider the pre-treatment aerobic fitness, medical comorbidities, and response to cancer treatment when prescribing exercise is recommended (66). In our study the participants could perform the exercise in a more personalized way within the prescribed dose of frequency, intensity, and duration. Recommendations about this were given both on the first test occasion for those being randomized to IG but also at the regular check-ups.

An adverse event due to increased volume in one of the limbs occurred in one participant after 6 weeks. Decongestive treatment was given, and the baseline measurements were achieved after some weeks. Even though there is a presumption that exercise may worsen LLL there are few adverse events reported in exercise studies including persons with LLL. This is probably due to that the exercise is recommended to start on a low intensity level and to be increased gradually (103). If the participants were not used to aerobic exercise, advice about the importance to start on a low level and increase gradually was also given in our study.

Methodological considerations

Strengths

In study I, II and III a comprehensive set of statistical methods to address the test-retest reliability of quantitative measurements was used (3) which is considered a strength in this thesis. Also, the relative value of the measurement errors both for a group of persons (SEM%) and in a single individual (SRD%) were evaluated. The relative values are easier to interpret and to compare with in other studies. There are very few studies that have evaluated the test-rest reliability of volume and local tissue water in healthy persons and in persons with LLL even though CMs to determine volume are common in LLL rehabilitation. Positively, concluded in this thesis is that volume and local tissue water can be reliably measured in healthy women and men (paper I) and in persons with mild to moderate LLL (paper II and III), also that impedance of ECF can be reliably measured in persons with mild to moderate LLL (paper II).

Local tissue water was assessed in 14 points located at different levels with the intention to cover different parts of the lower limbs. A standardized measurement protocol was developed to identify each of the points and this protocol was used in paper I, II and IV. There are only few studies evaluating local tissue water on the lower limbs and in these studies points were located on the foot and lower leg (75, 104). To evaluate local tissue water also on the thigh seems to be important because cancer related lymphedema seems to begin proximally in the lower limbs (17). The results in this thesis will thus contribute to new knowledge about different measurement locations on the lower limbs.

A strength was that a standardized measurement protocol was developed for CMs on the lower limbs and used in all papers in this thesis. This protocol is well described in the papers and in this thesis. To use a highly standardized measurement procedure is important (105) and contributes to achieve reliable measurements which is shown in paper I-III.

Another strength was that each lower limb was evaluated separately. In this way the results in this thesis can be used in persons with unilateral LLL as well as those with bilateral LLL. One aspect to be aware of when evaluating each lower limb separately is that a change in body weight will most likely result in a change in volume. So, together with CMs for volume there is also a need for assessments of body weight. By taking the weight in to account when evaluating changes in volume, a more accurate evaluation may be done.

A strength in paper IV, was that several measurement instruments and patient reported outcome measurements according to ICF were used. In this way both function and disabilities, such as activity limitations and participation restrictions were addressed. The between group analyses showed significant improvement in perceived lymphedema-related disability assessed by the Lymph-ICF-LL after the intervention, in favour of the exercise, which is of great interest. A further analysis of in which domain or domains improvements were perceived needs to be done. A disease specific HRQOL questionnaire was also used in study IV and significant improvements after the intervention was seen in the within group analyses. Further analysis will also be conducted to evaluate changes in each domain separately. Even though these two questionnaires are self-reported measures they reflect slightly different areas. To further evaluate how these questionnaires can be implemented in the clinic is of interest.

In study IV, an assessor blinded to group allocation performed most of the measurements after the 8-week intervention. This could also be considered a strength. However, the CMs and markings for the measurement points of local tissue water were both performed by CJ because in these measurement methods there are some manual steps which most likely will negatively affect the inter-rater reliability.

Limitations

Only persons with mild to moderate LLL were included in this thesis which could be considered a limitation. To use the results from this thesis in persons with severe LLL may not be correct because to measure a larger limb is more difficult. Therefore, to evaluate the test-retest reliability analyses of volume, local tissue water and impedance of ECF in persons with severe LLL would be valuable and to evaluate the efficacy and feasibility of exercise in these persons. A reason for including only persons with mild to moderate LLL is that mild to moderate LLL is more common in our clinic. There are only few persons with severe LLL most likely because of a structured rehabilitation process implemented in our clinic. A contributing factor may also be an increasing knowledge about LLL in health care professionals in our department and in clinics where the oncology treatment can cause LLL, resulting in early LLL diagnosis and start of treatment.

The limited number of men included in study II can also be considered a limitation. Our intention in study II was to evaluate the test-retest reliability separately for women and men, but since no discernible systematic differences between the sexes were found in the analyses and the limited number of potential participants, data for the participants were combined. An increased number of participants in study I might also have affected the systematic changes in the mean for the women in a positive way. But since the changes in the mean were small and usually occurred in only one of the lower limbs, we reasoned that the results were of value. Interestingly, no systematic changes in the mean in any of the measuring points for local tissue water were revealed in persons with LLL (paper II).

A limitation in study IV was the small number of participants. The interest in participating in the exercise study may be greater if the intervention took place closer to the cancer treatment (65) and the onset of LLL. However, some of the participants had been diagnosed with LLL several years ago and still found it interesting to participate to gain more knowledge about effects of moderate intensity exercise on the LLL. The inclusion was also affected by the COVID pandemic which forced us to interrupt the intervention for a couple of years. During this time, other rehabilitation units in the southern part of Sweden were contacted to be able to identify more potential participants. Based on this we believe that the number of participants is sufficient for a pilot RCT.

Another limitation was that some of the participants in study IV already at baseline were performing weekly moderate exercise. If the intervention takes place closer to finishing cancer treatment, there is more likely several potential participants not performing moderate intensity exercise regularly. To include persons already exercising was however accepted because of the limited knowledge about the effects of moderate exercise in persons with LLL (67-69, 103).

Conclusions

- CMs and TDC measurements are reliable in lower limbs of healthy women and men. Both methods can be recommended for a group of persons and in single persons. However, TDC points close to bone and tendons in men should be used with caution.
- Impedance of ECF, volume and local tissue water can be reliably measured in persons with mild to moderate, unilateral, or bilateral LLL. The measurement errors were acceptable in all three methods (i.e., arm-leg impedance ratios, CMs and TDC) indicating that real, clinical changes in lymphedema can be measured both for a group of persons and a single individual with LLL.
- The agreement was high between all measurement methods, but slightly higher between the V4 and V8 methods than between V4 and V12, and the test-retest reliability was equally high for all three methods. The V8 method can thus replace the V4 method when using CMs for volume in persons with LLL.
- Moderate intensity home-based bicycling exercise is feasible and improves local tissue water, lymphedema-related disability, physical fitness, and health related quality of life in persons with LLL. Regular check-ups for volume control and guidance are supportive.

Clinical implications

The findings from this thesis have several important clinical implications:

- By using standardized measurement protocols, volume, local tissue water and impedance of ECF can be reliably measured in persons with LLL and most likely in those at risk of LLL.
- Knowledge of the normal variability in CMs, TDC measurements and impedance ratios, will give higher confidence in the interpretation of changes in these measurements after treatment or self-care in persons with mild to moderate LLL.
- For early diagnosis of LLL both quantitative measurements and manual examination are recommended. A change in volume and local tissue water outside the limit for normal variation in a healthy population may aid prevention and early diagnoses in persons at risk of LLL after extensive lymph node dissection and radiation.
- To follow LLL over time and evaluate short-term or long-term effects of an intervention, both quantitative measurements and patient-reported outcomes according to ICF are recommended.
- CMs every 8th cm is recommended to replace CMs every 4th cm for volume in the management of LLL. The high agreement between these two methods and the equally high test-retest reliability and low measurement errors, makes the faster 8th cm method more attractive.
- Advice about home-based moderate intensity exercise in persons with LLL may be supported by an exercise logbook and a heart rate monitor besides oral and written information. Short regular follow-ups are supportive and recommended to detect possible adverse events because of the limited knowledge in this area.
- To support moderate exercise in persons treated for cancer and in persons with a chronic condition is important. The positive effects such as improved perception of lymphedema-related disability and health related quality of life together with increased physical fitness, support that exercise is beneficial without worsening the lymphedema. But future research is needed to confirm the results.

Future research

- The results from the pilot RCT evaluated in this thesis support that moderate intensity bicycling exercise can be performed without the risk of worsening LLL, on the contrary we found positive effects but due to the small sample size future research in this area is needed.
- To evaluate the effects and feasibility of moderate intensity exercise in persons short time after onset of LLL is of great interest. Future research in this area may also investigate which domains in perceived lymphedema-related disability and health related quality of life that seem to be affected and possible reason for this.
- There is limited knowledge about the experience of having LLL, the self-care needed and support from the health care. Based on this a qualitative study focusing on these experiences in persons with LLL would be of interest to increase the knowledge about this condition for health caregivers.
- Studies have shown that persons with LLL experience lower HRQOL compared to persons with upper limb lymphedema. There may be various reasons for this but more knowledge about this may facilitate a more person-centred rehabilitation in LLL management. Therefore, future research in this area is needed.
- Early diagnosis of cancer-related lymphedema and treatment is important to limit the swelling in the long-term. Research has shown that surveillance programs using quantitative measurement methods and manual examination for persons at risk of upper limb lymphedema can prevent progression of lymphedema. Research is needed to identify risk patients and time for onset of LLL following treatment for gynecological cancer, malignant melanoma, and urological cancer. A prospective, longitudinal study can form a base for a surveillance program for the prevention and early diagnosis of LLL and increase knowledge about the incidence/ prevalence of LLL in a population where such knowledge is lacking.

Acknowledgements

Först och främst vill jag tacka alla personer som har deltagit i de olika studierna i denna avhandling, utan er hade inte denna avhandling varit möjlig.

Jag vill också rikta ett stort tack till

Christina Brogårdh min huvudhandledare, under den senare halvan av min forskarutbildning. Du har varit ett stort stöd med all din kunskap om forskning och statistiska metoder, inte minst de olika analysmetoderna vid utvärdering av reliabilitetsstatistiken. Din stora kunskap och noggrannhet vi manusskrivning har varit ett stort stöd.

Karin Johansson, biträdande handledare och huvudhandledare under första halvan av min forskarutbildning. Ditt stora engagemang och breda kunskap inom området lymfödem som du delat med dig av har jag uppskattat. Din vana och stora erfarenhet vid manusskrivning har varit till stor hjälp.

Maria Bjurberg, biträdande handledare, som under hela min forskarutbildning varit mycket positiv, engagerad och gett stort stöd. Du har delat med dig av din breda kunskap och det uppskattar jag verkligen. Dina råd vid manusskrivning har varit lärorika.

Carina Lindh, min nuvarande chef, stort tack till dig som gjort det möjligt för mig att kunna gå denna forskarutbildning.

Anna Johnsson, fysioterapeut, PhD, och tidigare doktorandkollega, för att du ställde upp och gjorde slutmätningen i delarbete 4. Även dina råd och uppmuntran under doktorandtiden har varit viktiga.

Marie Hurtig och Carolina Larsson, fysioterapeuter på Centralsjukhuset i Kristianstad, i samband med mätningar av forskningsdeltagare hos er. Ni ordnade så jag fick ett rum och utrustning. Tack för er uppmuntran och positiva inställning.

Barbro Jönsson, fysioterapeut och Christer Jönsson, medarbetare på Lasarettet i Ystad, för all er hjälp i samband med mätningar av forskningsdeltagare hos er. Tack för er hjälp med mätutrustning och ett rum att vara i. Er positiva inställning och engagemang har känts bra.

Inger Nilsson, för att jag fick låna ett rum på din salong så att mätningar av personer i delarbete 1 kunde genomföras i byn där många bodde. Jag uppskattar verkligen din positiva inställning och stora engagemang.

Michael Miller, fysioterapeut, PhD, för din språkgranskning av delarbetena och av kappan.

Statistiker vid Kliniska Studier Sverige Forum Söder, för råd kring statistiken i delstudie 1 och 3.

Katarina Blom, PhD och tidigare doktorandkollega, tack för alla intressanta diskussioner vi har haft om mätmetoder vid lymfödem, alla trevliga stunder på konferenser både i Sverige och utomlands. Jag värdesätter ditt engagemang och ser fram emot fortsatt samarbete.

Agneta Hagren, nuvarande doktorandkollega, tack för din support och feedback i samband med studierna och givande diskussioner om mätning av lymfödem. Uppskattar din kritiska blick. Ser fram emot fortsatt samarbete.

Kollegor på Lymfödemmottagningen och Cancerrehabiliteringsmottagningen SUS Lund och Malmö, för att ni har varit intresserade av min forskning och tack för alla foton ni ställt upp på.

Nuvarande och tidigare doktorandkollegor, samt docenter och professorer i forskargrupperna Rehabilitering och hållbar hälsa samt Människan i rörelse, tack för all uppmuntran och lärorika samtal.

Håkan Brorson, läkare, professor, för att du gjorde formeln för V8 metoden så att den blivit tillgänglig för kollegor och för att du så generöst delar med dig av din stora kunskap.

Tapani Lahtinen, läkare och medarbetare på Delphin Technologies, för alla intressanta samtal om mätning av lokal vävnadsvätska och extracellulär vätska, du har ett stort engagemang.

Kollegorna inom lymfödemvården i södra regionen, för att ni har varit intresserade av min forskning och de livliga workshops med lymfödemmätning som vi haft tillsammans.

Stefan, för allt stöd du har gett mig under forskarutbildningen, all datasupport jag har fått har varit otroligt värdefull. Du har alltid lyssnat på mig, engagerat dig och gett kloka råd. Neo, för att du har stöttat mig på olika sätt men också med din datakunskap, det uppskattar jag verkligen.

Min syster Anna, för våra samtal och all klokskap som du delar med dig av.

Min pappa och bror samt, övrig släkt och vänner som alltid varit intresserade. Särskilt tack till er som ställde upp på fotot till omslaget.

This thesis was supported by grants from the Swedish Cancer Society, Vårdakademin at Skåne University Hospital and the Swedish Association of Chronic Oedema.

References

1. Martin-Almedina S, Mortimer PS, Ostergaard P. Development and physiological functions of the lymphatic system: insights from human genetic studies of primary lymphedema. Physiol Rev. 2021;101(4):1809-71.
2. Suami H. Anatomical Theories of the Pathophysiology of Cancer-Related Lymphoedema. Cancers (Basel). 2020;12(5).
3. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. Am J Phys Med Rehabil. 2005;84(9):719-23.
4. Downham DHALJ. Reliability of measurements in medical research and clinical practice. In: Ray P LA, editor. Studies in Multidisciplinarity 3. Amsterdam: Elsevier; 2005. p. 147-63.
5. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Phys Ther. 2016;96(12):1965-81.
6. Hayes SC, Singh B, Reul-Hirche H, Bloomquist K, Johansson K, Jönsson C, et al. The Effect of Exercise for the Prevention and Treatment of Cancer-Related Lymphedema: A Systematic Review with Meta-analysis. Med Sci Sports Exerc. 2022;54(8):1389-99.
7. von der Weid PY, Zawieja DC. Lymphatic smooth muscle: the motor unit of lymph drainage. Int J Biochem Cell Biol. 2004;36(7):1147-53.
8. Greene AK, Slavin SA, Brorson H. Lymphedema: Presentation, Diagnosis, and Treatment. Springer International Publishing Switzerland 2015. DOI 10.1007/978-3-319-14493-1
9. Neuberger M, Schmidt L, Wessels F, Linke M, Muller C, Westhoff N, et al. Onset and burden of lower limb lymphedema after radical prostatectomy: a cross-sectional study. Support Care Cancer. 2022;30(2):1303-13.
10. Yoshihara M, Shimono R, Tsuru S, Kitamura K, Sakuda H, Oguchi H, et al. Risk factors for late-onset lower limb lymphedema after gynecological cancer treatment: A multi-institutional retrospective study. Eur J Surg Oncol. 2020;46(7):1334-8.
11. Geoffrey E. Hespe MDN, Badak J. Mehrara. Pathophysiology of Lymphedema. In: Arin K. Greene SAS, Håkan Brorson editor. Lymphedema Presentation, Diagnosis, and Treatment: Springer International Publishing Switzerland 2015; 2015. p. 9-18.
12. Johansson K, Branje E. Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis. Acta Oncol. 2010;49(2):166-73.

13. Lymphoedema Framework. Best practice for the management of lymphoedema. International consensus.: London: MEP Ltd, 2006; 2006 [Available from: https://woundsinternational.com/wp-content/uploads/sites/8/2023/02/4335b42108c9c1fd8b4af44f3db4b2c2.pdf.
14. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. J Am Acad Dermatol. 2017;77(6):1009-20.
15. Smeltzer DM, Stickler GB, Schirger A. Primary lymphedema in children and adolescents: a follow-up study and review. Pediatrics. 1985;76(2):206-18.
16. Hayes SC, Janda M, Ward LC, Reul-Hirche H, Steele ML, Carter J, et al. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. Gynecol Oncol. 2017;146(3):623-9.
17. Biglia N, Librino A, Ottino MC, Panuccio E, Daniele A, Chahin A. Lower limb lymphedema and neurological complications after lymphadenectomy for gynecological cancer. Int J Gynecol Cancer. 2015;25(3):521-5.
18. Carlson JW, Kauderer J, Hutson A, Carter J, Armer J, Lockwood S, et al. GOG 244-The lymphedema and gynecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients. Gynecol Oncol. 2020;156(2):467-74.
19. Friedman JF, Sunkara B, Jehnsen JS, Durham A, Johnson T, Cohen MS. Risk factors associated with lymphedema after lymph node dissection in melanoma patients. Am J Surg. 2015;210(6):1178-84; discussion 84.
20. Hyngstrom JR, Chiang YJ, Cromwell KD, Ross MI, Xing Y, Mungovan KS, et al. Prospective assessment of lymphedema incidence and lymphedema-associated symptoms following lymph node surgery for melanoma. Melanoma Res. 2013;23(4):290-7.
21. Clinckaert A, Callens K, Cooreman A, Bijnens A, Moris L, Van Calster C, et al. The Prevalence of Lower Limb and Genital Lymphedema after Prostate Cancer Treatment: A Systematic Review. Cancers (Basel). 2022;14(22).
22. Peters AM, Mortimer PS. "Latent" and "constitutional" lymphedema, useful terms to complement the terms "primary" and "secondary" lymphedema. J Vasc Surg Venous Lymphat Disord. 2021;9(5):1089-92.
23. Schaverien MV, Munnoch DA, Brorson H. Liposuction Treatment of Lymphedema. Semin Plast Surg. 2018;32(1):42-7.
24. Lindqvist E, Wedin M, Fredrikson M, Kjølhede P. Lymphedema after treatment for endometrial cancer - A review of prevalence and risk factors. Eur J Obstet Gynecol Reprod Biol. 2017;211:112-21.
25. Greene AK. Primary lymphedema. Greene AK, Slavin SA, Brorson H. Lymphedema: Presentation, Diagnosis, and Treatment (pp 59-77). Springer International Publishing Switzerland 2015. DOI 10.1007/978-3-319-14493-1
26. Tiwari A, Myint F, Hamilton G. Management of lower limb lymphoedema in the United Kingdom. Eur J Vasc Endovasc Surg. 2006;31(3):311-5.

27. Nationellt Vårdprogram Cancerrehabilitering. Regionala Cancercentrum i samverkan (RCC) 2021 [Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/cancerrehabilitering/vardprogram/Symtom-och-symtomlindring/#chapter-9-8-Lymfodem.
28. Lahtinen T, Seppälä J, Viren T, Johansson K. Experimental and Analytical Comparisons of Tissue Dielectric Constant (TDC) and Bioimpedance Spectroscopy (BIS) in Assessment of Early Arm Lymphedema in Breast Cancer Patients after Axillary Surgery and Radiotherapy. Lymphat Res Biol. 2015;13(3):176-85.
29. Werngren-Elgström M, Lidman D. Lymphoedema of the lower extremities after surgery and radiotherapy for cancer of the cervix. Scand J Plast Reconstr Surg Hand Surg. 1994;28(4):289-93.
30. Dean SM, Valenti E, Hock K, Leffler J, Compston A, Abraham WT. The clinical characteristics of lower extremity lymphedema in 440 patients. J Vasc Surg Venous Lymphat Disord. 2020;8(5):851-9.
31. Brorson H, Svensson B, Ohlin K. Volume measurements and follow-up. Greene AK, Slavin SA, Brorson H. Lymphede: Presentation, Diagnosis, and Treatment (pp 115-122). Springer International Publishing Switzerland 2015. DOI. 10.1007/978-3-319-14493-1
32. Huang J, Yu N, Wang X, Long X. Incidence of lower limb lymphedema after vulvar cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(46):e8722.
33. Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. Cancer. 2010;116(22):5138-49.
34. Stanton AW, Northfield JW, Holroyd B, Mortimer PS, Levick JR. Validation of an optoelectronic limb volumeter (Perometer). Lymphology. 1997;30(2):77-97.
35. Sharkey AR, King SW, Kuo RY, Bickerton SB, Ramsden AJ, Furniss D. Measuring Limb Volume: Accuracy and Reliability of Tape Measurement Versus Perometer Measurement. Lymphat Res Biol. 2018;16(2):182-6.
36. Stanton AW, Badger C, Sitzia J. Non-invasive assessment of the lymphedematous limb. Lymphology. 2000;33(3):122-35.
37. Sawan S, Mugnai R, Lopes Ade B, Hughes A, Edmondson RJ. Lower-limb lymphedema and vulval cancer: feasibility of prophylactic compression garments and validation of leg volume measurement. Int J Gynecol Cancer. 2009;19(9):1649-54.
38. Tidhar D, Armer JM, Deutscher D, Shyu CR, Azuri J, Madsen R. Measurement Issues in Anthropometric Measures of Limb Volume Change in Persons at Risk for and Living with Lymphedema: A Reliability Study. J Pers Med. 2015;5(4):341-53.
39. Mayrovitz HN, Macdonald J, Davey S, Olson K, Washington E. Measurement decisions for clinical assessment of limb volume changes in patients with bilateral and unilateral limb edema. Phys Ther. 2007;87(10):1362-8.
40. Karlsson K, Johansson K, Nilsson-Wikmar L, Brogårdh C. Tissue Dielectric Constant and Water Displacement Method Can Detect Changes of Mild Breast Cancer-Related Arm Lymphedema. Lymphat Res Biol. 2022;20(3):325-34.

41. Blom KY, Johansson KI, Nilsson-Wikmar LB, Brogårdh CB. Early intervention with compression garments prevents progression in mild breast cancer-related arm lymphedema: a randomized controlled trial. Acta Oncol. 2022;61(7):897-905.
42. Johansson K, Jönsson C, Björk-Eriksson T. Compression Treatment of Breast Edema: A Randomized Controlled Pilot Study. Lymphat Res Biol. 2020;18(2):129-35.
43. Tugral A, Viren T, Bakar Y. Tissue dielectric constant and circumference measurement in the follow-up of treatment-related changes in lower-limb lymphedema. Int Angiol. 2018;37(1):26-31.
44. Cornish BH, Thomas BJ, Ward LC, Hirst C, Bunce IH. A new technique for the quantification of peripheral edema with application in both unilateral and bilateral cases. Angiology. 2002;53(1):41-7.
45. Cornish B. Bioimpedance analysis: scientific background. Lymphat Res Biol. 2006;4(1):47-50.
46. Steele ML, Janda M, Vagenas D, Ward LC, Cornish BH, Box R, et al. Normative Interlimb Impedance Ratios: Implications for Early Diagnosis of Uni- and Bilateral, Upper and Lower Limb Lymphedema. Lymphat Res Biol. 2018;16(6):559-66.
47. Klernäs P, Johnsson A, Horstmann V, Kristjanson LJ, Johansson K. Lymphedema Quality of Life Inventory (LyQLI)-Development and investigation of validity and reliability. Qual Life Res. 2015;24(2):427-39.
48. Klernäs P, Johnsson A, Horstmann V, Johansson K. Health-related quality of life in patients with lymphoedema - a cross-sectional study. Scand J Caring Sci. 2018;32(2):634-44.
49. Devoogdt N, De Groef A, Hendrickx A, Damstra R, Christiaansen A, Geraerts I, et al. Lymphoedema Functioning, Disability and Health Questionnaire for Lower Limb Lymphoedema (Lymph-ICF-LL): reliability and validity. Phys Ther. 2014;94(5):705-21.
50. Appelgren M, Sackey H, Wengström Y, Johansson K, Ahlgren J, Andersson Y, et al. Patient-reported outcomes one year after positive sentinel lymph node biopsy with or without axillary lymph node dissection in the randomized SENOMAC trial. Breast. 2022;63:16-23.
51. Stolldorf DP, Dietrich MS, Ridner SH. Symptom Frequency, Intensity, and Distress in Patients with Lower Limb Lymphedema. Lymphat Res Biol. 2016;14(2):78-87.
52. Rowlands IJ, Beesley VL, Janda M, Hayes SC, Obermair A, Quinn MA, et al. Quality of life of women with lower limb swelling or lymphedema 3-5 years following endometrial cancer. Gynecol Oncol. 2014;133(2):314-8.
53. Dunberger G, Lindquist H, Waldenström AC, Nyberg T, Steineck G, Åvall-Lundqvist E. Lower limb lymphedema in gynecological cancer survivors--effect on daily life functioning. Support Care Cancer. 2013;21(11):3063-70.
54. Cromwell KD, Chiang YJ, Armer J, Heppner PP, Mungovan K, Ross MI, et al. Is surviving enough? Coping and impact on activities of daily living among melanoma patients with lymphoedema. Eur J Cancer Care (Engl). 2015;24(5):724-33.

55. Carter J, Huang HQ, Armer J, Carlson JW, Lockwood S, Nolte S, et al. GOG 244 - The Lymphedema and Gynecologic cancer (LeG) study: The impact of lower-extremity lymphedema on quality of life, psychological adjustment, physical disability, and function. Gynecol Oncol. 2021;160(1):244-51.
56. World Health Organization. International Classification of Functioning, disability and health: ICF. Geneva: World Health Organization; 2001.
57. Brogårdh C, Lexell J. ICF and neurorehabilitation. NeuroRehabilitation. 2015;36(1):1-3.
58. Lexell J, Brogårdh C. The use of ICF in the neurorehabilitation process. NeuroRehabilitation. 2015;36(1):5-9.
59. Lasinski BB, McKillip Thrift K, Squire D, Austin MK, Smith KM, Wanchai A, et al. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. Pm r. 2012;4(8):580-601.
60. Cancerrehabilitering Regional tillämpning för Södra sjukvårdsregionen av nationellt vårdprogram, avsnitt 9.8 Lymfödem 2022 [Available from: https://cancercentrum.se/globalassets/vara-uppdrag/rehabilitering-palliativ-vard/syd/regionalt-tillampning-for-lymfodem_nvp-cancerrehab_version-2.0.pdf.
61. Bonn SE, Sjölander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al. Physical activity and survival among men diagnosed with prostate cancer. Cancer Epidemiol Biomarkers Prev. 2015;24(1):57-64.
62. Cormie P, Zopf EM, Zhang X, Schmitz KH. The Impact of Exercise on Cancer Mortality, Recurrence, and Treatment-Related Adverse Effects. Epidemiol Rev. 2017;39(1):71-92.
63. Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis. JNCI Cancer Spectr. 2020;4(1):pkz080.
64. Orsini N, Mantzoros CS, Wolk A. Association of physical activity with cancer incidence, mortality, and survival: a population-based study of men. Br J Cancer. 2008;98(11):1864-9.
65. Tucker K, Staley SA, Clark LH, Soper JT. Physical Activity: Impact on Survival in Gynecologic Cancer. Obstet Gynecol Surv. 2019;74(11):679-92.
66. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26.
67. Lindquist H, Enblom A, Dunberger G, Nyberg T, Bergmark K. WATER EXERCISE COMPARED TO LAND EXERCISE OR STANDARD CARE IN FEMALE CANCER SURVIVORS WITH SECONDARY LYMPHEDEMA. Lymphology. 2015;48(2):64-79.
68. Dionne A, Goulet S, Leone M, Comtois AS. Aquatic Exercise Training Outcomes on Functional Capacity, Quality of Life, and Lower Limb Lymphedema: Pilot Study. J Altern Complement Med. 2018;24(9-10):1007-9.
69. Do JH, Choi KH, Ahn JS, Jeon JY. Effects of a complex rehabilitation program on edema status, physical function, and quality of life in lower-limb lymphedema after gynecological cancer surgery. Gynecol Oncol. 2017;147(2):450-5.

70. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451-62.
71. Thomis S, Dams L, Fourneau I, De Vrieze T, Nevelsteen I, Neven P, et al. Correlation Between Clinical Assessment and Lymphofluoroscopy in Patients with Breast Cancer-Related Lymphedema: A Study of Concurrent Validity. Lymphat Res Biol. 2020;18(6):539-48.
72. Frändin. Assessment of physical activity, fitness and performance in 76-year-olds. Scandinavian Journal of Medicine & Science in Sports 1994;4:41-6.
73. Sitzia J. Volume measurement in lymphoedema treatment: examination of formulae. Eur J Cancer Care (Engl). 1995;4(1):11-6.
74. Nuutinen J, Ikäheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. Physiol Meas. 2004;25(2):447-54.
75. Mayrovitz HN. Assessing Upper and Lower Extremities Via Tissue Dielectric Constant: Suitability of Single Versus Multiple Measurements Averaged. Lymphat Res Biol. 2019;17(3):316-21.
76. Ward LC, Dylke E, Czerniec S, Isenring E, Kilbreath SL. Reference ranges for assessment of unilateral lymphedema in legs by bioelectrical impedance spectroscopy. Lymphat Res Biol. 2011;9(1):43-6.
77. Åstrand P-O. Work tests with the bicycle ergometer [Available from: https://monarksportsmed.com/wp-content/uploads/2018/11/AstrandNEW.pdf.
78. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81.
79. Ekblom-Bak E, Björkman F, Hellenius ML, Ekblom B. A new submaximal cycle ergometer test for prediction of VO2max. Scand J Med Sci Sports. 2014;24(2):319-26.
80. Klernäs P, Johnsson A, Boyages J, Brorson H, Munnoch A, Johansson K. Test of Responsiveness and Sensitivity of the Questionnaire "Lymphedema Quality of Life Inventory". Lymphat Res Biol. 2018;16(3):300-8.
81. Kostanjsek N. Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems. BMC Public Health. 2011;11 Suppl 4(Suppl 4):S3.
82. Scott J, Huskisson EC. Graphic representation of pain. Pain. 1976;2(2):175-84.
83. Johansson K, Albertsson M, Ingvar C, Ekdahl C. Effects of compression bandaging with or without manual lymph drainage treatment in patients with postoperative arm lymphedema. Lymphology. 1999;32(3):103-10.
84. Jönsson C, Johansson K. The effects of pole walking on arm lymphedema and cardiovascular fitness in women treated for breast cancer: a pilot and feasibility study. Physiother Theory Pract. 2014;30(4):236-42.

85. Mellor RH, Bush NL, Stanton AW, Bamber JC, Levick JR, Mortimer PS. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema. Breast J. 2004;10(6):496-503.
86. Hopkins WG. Measures of reliability in sports medicine and science. Sports Med. 2000;30(1):1-15.
87. Fleiss JL. The Design and Analysis of Clinical Experiments. New York: John Wiley & Sons; 1986.
88. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999;8(2):135-60.
89. Flansbjer UB, Holmbäck AM, Downham D, Lexell J. What change in isokinetic knee muscle strength can be detected in men and women with hemiparesis after stroke? Clin Rehabil. 2005;19(5):514-22.
90. te Slaa A, Mulder P, Dolmans D, Castenmiller P, Ho G, van der Laan L. Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements. Phlebology. 2011;26(1):14-9.
91. Bakar Y, Özdemir Ö C, Sevim S, Duygu E, Tuğral A, Sürmeli M. Intra-observer and inter-observer reliability of leg circumference measurement among six observers: a single blinded randomized trial. J Med Life. 2017;10(3):176-81.
92. Tan CW, Coutts F, Bulley C. Measurement of lower limb volume: agreement between the vertically oriented perometer and a tape measure method. Physiotherapy. 2013;99(3):247-51.
93. Czerniec SA, Ward LC, Refshauge KM, Beith J, Lee MJ, York S, et al. Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. Cancer Invest. 2010;28(1):54-62.
94. Chen YW, Tsai HJ, Hung HC, Tsauo JY. Reliability study of measurements for lymphedema in breast cancer patients. Am J Phys Med Rehabil. 2008;87(1):33-8.
95. De Vrieze T, Gebruers N, Tjalma WA, Nevelsteen I, Thomis S, De Groef A, et al. What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods. Clin Rehabil. 2019;33(7):1221-32.
96. De Vrieze T, Gebruers N, Nevelsteen I, De Groef A, Tjalma WAA, Thomis S, et al. Reliability of the MoistureMeterD Compact Device and the Pitting Test to Evaluate Local Tissue Water in Subjects with Breast Cancer-Related Lymphedema. Lymphat Res Biol. 2020;18(2):116-28.
97. Kaulesar Sukul DM, den Hoed PT, Johannes EJ, van Dolder R, Benda E. Direct and indirect methods for the quantification of leg volume: comparison between water displacement volumetry, the disk model method and the frustum sign model method, using the correlation coefficient and the limits of agreement. J Biomed Eng. 1993;15(6):477-80.
98. Sander AP, Hajer NM, Hemenway K, Miller AC. Upper-extremity volume measurements in women with lymphedema: a comparison of measurements obtained via water displacement with geometrically determined volume. Phys Ther. 2002;82(12):1201-12.

99. Gjorup C, Zerahn B, Hendel HW. Assessment of volume measurement of breast cancer-related lymphedema by three methods: circumference measurement, water displacement, and dual energy X-ray absorptiometry. Lymphat Res Biol. 2010;8(2):111-9.

100. McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. Med Sci Sports Exerc. 2019;51(6):1252-61.

101. Johansson K, Hayes S, Speck RM, Schmitz KH. Water-based exercise for patients with chronic arm lymphedema: a randomized controlled pilot trial. Am J Phys Med Rehabil. 2013;92(4):312-9.

102. Gildea GC, Spence RR, Jones TL, Turner JC, Macdonald ER, Hayes SC, et al. Barriers, facilitators, perceptions and preferences influencing physical activity participation, and the similarities and differences between cancer types and treatment stages - A systematic rapid review. Prev Med Rep. 2023;34:102255.

103. Katz E, Dugan NL, Cohn JC, Chu C, Smith RG, Schmitz KH. Weight lifting in patients with lower-extremity lymphedema secondary to cancer: a pilot and feasibility study. Arch Phys Med Rehabil. 2010;91(7):1070-6.

104. Jensen MR, Birkballe S, Nørregaard S, Karlsmark T. Validity and interobserver agreement of lower extremity local tissue water measurements in healthy women using tissue dielectric constant. Clin Physiol Funct Imaging. 2012;32(4):317-22.

105. Russo S, Walker JL, Carlson JW, Carter J, Ward LC, Covens A, et al. Standardization of lower extremity quantitative lymphedema measurements and associated patient-reported outcomes in gynecologic cancers. Gynecol Oncol. 2021;160(2):625-32.

Appendix

Characteristics for the participants in study II-IV according to LLL status: exceeding the threshold for volume difference of ≥5% (29), higher local tissue water (TDC) (exceeding mean +3SD in healthy women and men) (paper I) and exceeding threshold for extracellular fluid (ECF) (46) and the presence of perceived heaviness and tightness in the affected limb or limbs.

Clinical lymphedema characteristic of the participants in study II-IV.

	Study II and III (n=42)	Study IV	
		Intervention group (n=16)	Control group (n=11)
Subjective assessments			
Perception of heaviness, n (%)			
MA limb	18 (43)	8 (50)	5 (46)
LA limb	4 (10)	0	0
Perception of tightness, n (%)			
MA limb	8 (19)	7 (44)	3 (27)
LA limb	1 (3)	0	0
Objective assessments			
Increased thickness of subcutaneous tissue, n (%)			
MA limb	42 (100)	16 (100)	11 (100)
LA limb	5 (12)	0	0
Interlimb volume difference ≥ 5%, n (%)	26 (62)	12 (75)	7 (64)
Increased TDC in ≥ one measuring point, n (%)			
MA limb	31 (74)	12 (75)	10 (91)
LA limb	16 (38)		
Arm-leg impedance ratio exceeding the threshold for lymphedema, n (%)			
MA limb	16 (38)	4 (25)	0
LA limb	4 (10)		
MA, more affected; LA, less affected; TDC, tissue dielectric constant			

Cykelstudien Initialer……. Nr…….

FUNKTIONSPÅVERKAN VID BENLYMFÖDEM – BEN

Datum …………………….

Lymfödem i ett eller båda benen kan påverka både fysiskt och mentalt.

Detta frågeformulär innehåller 28 frågor och är baserat på information som lämnats av personer som har benlymfödem.

Intill varje fråga finns en 10 cm lång vågrät linje. Vid ändpunkterna på varje linje står orden ”Mycket bra” och ”Inte alls”. Var vänlig gör en liten lodrät markering på varje vågrät linje. Markeringen anger graden av besvär eller aktivitetsnedsättning på grund av lymfödem i ett eller båda benen.

Till exempel	**Mycket bra**	**Inte alls**	**Ej aktuellt**
Hur bra kan du utföra trädgårdsarbete?			○

Sätt en lodrät markering vid den vänstra ändpunkten, om du kan utföra trädgårdarbete utan problem.

	Mycket bra	**Inte alls**	**Ej aktuellt**
Hur bra kan du utföra trädgårdsarbete?			○

Sätt en lodrät markering åt höger på den vågräta linjen om du har stora problem att utföra trädgårdsarbete. Markera i ringen längst till höger, om du inte har trädgård eller av annan anledning inte ägnat dig åt trädgårdsarbete.

Var vänlig ange hur det varit under **de senaste två veckorna** och lämna inte någon fråga obesvarad.

Ange din egen uppfattning och diskutera inte med någon i din omgivning.

Cykelstudien Initialer……. Nr…….

Sid 1

Fysiska problem

På grund av lymfödem i ett eller båda benen:

	Inte alls	Mycket
1. Gör det ont	├	┤
2. Känns huden spänd	├	┤
3. Känns stickningar	├	┤
4. Pågående eller regelbundet återkommande infektioner	├	┤
5. Känns stelt (nedsatt rörlighet)	├	┤
6. Känns tungt	├	┤

Mentala problem

På grund av lymfödem i ett eller båda benen känner jag:

	Inte alls	Mycket
7. Bristande självförtroende	├	┤
8. Känner mig ledsen	├	┤
9. Känner mig mindre attraktiv	├	┤
10. Känner mig frustrerad (spänd)	├	┤
11. Osäkerhet inför framtiden (t.ex arbetssituationen)	├	┤
12. Besviken på sjukvården (t.ex brist på information)	├	┤

Sid 2 →

Sid 2

<u>Arbete, hushållsaktiviteter</u>

På grund av lymfödem i ett eller båda benen:

	Inte alls	Mycket	Ej aktuellt
13. Har jag blivit mer beroende av andra			
14. Fått svårt att organisera olika saker (t.ex samman-komster, uppdrag)			
15. Svårt med hushållsarbete			○

<u>Fysisk förmåga</u>

Hur bra kan du:

	Mycket bra	Inte alls	Ej aktuellt
16. Sitta en längre stund			
17. Stå en längre stund			
18. Knäböja			
19. Gå mer än 2km			
20. Cykla			○
21. Köra bil			○
22. Gå i trappor			○

Sid 3 →

Sid 3

<u>Sociala aktiviteter</u>

Hur bra går det att:

	Mycket bra	Inte alls	Ej aktuellt
23. Yrkesarbeta	├	┤	○
Yrke…………………………………..			
24. Delta i sport	├	┤	○
Vilken/vilka……………………….			
25. Genomföra fritidsaktivitet	├	┤	○
26. Ha socialt umgänge	├	┤	○
27. Bära fritt val av kläder	├	┤	
28. Åka på semester	├	┤	○

Tack för din medverkan!

Frågeformulär om hur lymfödemet påverkar din livskvalitet

Detta frågeformulär tar upp frågor om på vilket sätt lymfödem kan påverka din livskvalitet och dagliga aktiviteter.

Du kan ha erfarenhet av mycket lätt lymfödem, måttliga eller svåra besvär. Du kan ha haft lymfödem kort eller lång tid.

Enkäten är indelad i tre dimensioner

- Fysisk
- Psykosocial
- Praktisk

Var snäll och svara på dessa frågor endast i den mån de **berör ditt lymfödem**

Tänk på ditt lymfödem och din livskvalitet under de **senaste 4 veckorna.**
När det gäller frågor som är exempelvis årstidsbundna, kan du tänka på hur det var det **senaste året.**

Ringa in det svar som bäst motsvarar dina upplevelser. **Försök svara på alla frågor.**

Om du inte tycker att de beskrivna besvären eller problemen berör dig, var snäll och ringa in “Inget” i svarskolumnen.

	Fysiska besvär på grund av lymfödem	**Hur mycket påverkar dessa besvär din livskvalitet?**			
1	Smärta/värk i lymfödemområdet	Inget	Lite	En del	Mycket
2	Obehagskänsla i lymfödemområdet	Inget	Lite	En del	Mycket
3	Tyngdkänsla i lymfödemområdet	Inget	Lite	En del	Mycket
4	Stickningar/domningar i lymfödemområdet	Inget	Lite	En del	Mycket
5	Brännande känsla/hetta i lymfödemområdet	Inget	Lite	En del	Mycket
6	Svullnad/spänningskänsla i lymfödemområdet	Inget	Lite	En del	Mycket
7	Hudproblem i lymfödemområdet	Inget	Lite	En del	Mycket
8	Sömnsvårigheter på grund av den svullna kroppsdelen	Inget	Lite	En del	Mycket
9	Rörelsesvårigheter på grund av lymfödemet	Inget	Lite	En del	Mycket
10	Blir påmind om den svullna kroppsdelen hela tiden	Inget	Lite	En del	Mycket
11	Känner minskad styrka i den svullna kroppsdelen	Inget	Lite	En del	Mycket
12	Rosfeber (erysipelas)	Inget	Lite	En del	Mycket

	Psykosociala problem på grund av lymfödem	Hur mycket påverkar dessa problem din livskvalitet?			
13	Känsla av irritation/frustration	Inget	Lite	En del	Mycket
14	Känner oro för huruvida lymfödemet blir värre eller inte	Inget	Lite	En del	Mycket
15	Generad för lymfödemet/kompressionsdelen/strumpan	Inget	Lite	En del	Mycket
16	Förändringar av hur jag ser på mig själv	Inget	Lite	En del	Mycket
17	Känner nedstämdhet	Inget	Lite	En del	Mycket
18	Att inte kunna göra de saker jag brukade tycka om att göra	Inget	Lite	En del	Mycket
19	Oroar mig för när jag bör uppsöka medicinsk vård	Inget	Lite	En del	Mycket
20	Tänker mycket på mitt tillstånd	Inget	Lite	En del	Mycket
21	Orolig för hur lymfödemet påverkar mina befintliga relationer	Inget	Lite	En del	Mycket
22	Oro för hur lymfödemet kan påverka nya relationer	Inget	Lite	En del	Mycket
23	Förändringar av mina sexuella känslor och intimitet	Inget	Lite	En del	Mycket
24	Känner mig obekväm eller generad i mina sport- och hobbyaktiviteter	Inget	Lite	En del	Mycket
25	Känner mig obekväm eller generad att delta i aktiviteter tillsammans med vänner, arbetskamrater etc.	Inget	Lite	En del	Mycket
26	Måste be om hjälp i olika situationer	Inget	Lite	En del	Mycket
27	Besvärad av förändringar i mitt utseende	Inget	Lite	En del	Mycket
28	Att behöva svara på frågor om den svullna kroppsdelen	Inget	Lite	En del	Mycket

	Praktiska problem på grund av lymfödem	Hur mycket påverkar dessa problem din livskvalitet?
29	Personlig vård (t.ex. klä på mig, vårda håret, fotvård)	Inget Lite En del Mycket
30	Hemmets skötsel/vardagsaktiviteter, sport- och hobbyaktiviteter	Inget Lite En del Mycket
31	Aktiviteter på jobbet	Inget Lite En del Mycket
32	Lära mig göra saker på ett annat sätt	Inget Lite En del Mycket
33	Har mindre ork att utföra praktiska saker (t.ex. personlig vård, hemmets skötsel eller på jobbet)	Inget Lite En del Mycket
34	Kostnader för att klara lymfödemet (t.ex. kläder, skor, behandlingar, kompressionsmaterial)	Inget Lite En del Mycket
35	Hitta fungerande kompressionsmaterial (t.ex. strumpa, ärm, handske)	Inget Lite En del Mycket
36	Åka längre sträckor med bil, tåg, flyg etc.	Inget Lite En del Mycket
37	Hitta bekväma/snygga kläder och skor, rätt storlek och material	Inget Lite En del Mycket
38	Begränsningar i att vistas i varm väderlek/solsken	Inget Lite En del Mycket
39	Den ständiga egenvård jag måste ägna mig åt för att förhindra lymfödemet från att försämras	Inget Lite En del Mycket
40	Skaffa information om hur jag ska klara av lymfödemet	Inget Lite En del Mycket
41	Vara beredd på akuta situationer (t.ex. alltid ha ett recept på antibiotika till hands)	Inget Lite En del Mycket

42. Har detta varit en typisk fyraveckorsperiod för dig, avseende ditt lymfödem?

Ja ( ) **Nej ( )**

43. Om du svarat "**Nej**", hur har denna fyraveckorsperiod varit (kryssa i ett alternativ)

Mycket värre ( ) **Värre ( )** **Bättre ( )** **Mycket bättre ( ) än vanligt**

44. Tänk igenom hur ditt lymfödem påverkat dig övergripande de senaste fyra veckorna och ringa in den siffra som bäst överensstämmer med din livskvalitet.

0	1	2	3
Mycket dålig			**Mycket bra**

45. Om du tar hänsyn till alla delar av ditt liv, hur skulle du beskriva din livskvalitet under de senaste fyra veckorna? Ringa in den siffra som bäst överensstämmer med din övergripande livskvalitet.

0	1	2	3
Mycket dålig			**Mycket bra**

Var vänlig kontrollera att du svarat på alla frågor.

Tack för att du tog dig tid att fylla i formuläret!

Printed by Media-Tryck, Lund 2023 NORDIC SWAN ECOLABEL 3041 0903

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LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Health Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2023:137
ISBN 978-91-8021-479-7
ISSN 1652-8220

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