Early diagnosis, treatment, and Health-Related Quality of Life in women with mild Breast Cancer-Related Lymphedema.

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LUND
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Abstract

Background: Early diagnosis and treatment of Breast Cancer-Related Lymphedema (BCRL) are important to prevent lymphedema progress and impact on Health-Related Quality of Life (HRQOL). The treatment includes self-care and treatment with compression garment. In mild BCRL, the lymphedema can be local, without an increase in arm volume. Tissue Dielectric Constant (TDC), measuring local tissue water in skin and subcutis, had not been used for diagnosis and to evaluate treatment in mild BCRL before. Also, knowledge about the effect of wearing a compression garment and its impact on HRQOL was unknown. The overall aim of this thesis was to evaluate diagnostic methods, treatment, and HRQOL in women with mild BCRL.

Methods: Women treated with axillary node dissection and diagnosed with mild BCRL were included. In paper I (n=72), the proportion of mild BCRL detected with TDC and/or Water Displacement Method (WDM) in combination with skin palpation at diagnosis were evaluated. Also, association between TDC and WDM measurements and lymphedema related factors were examined. In paper II, (n= 46), changes in local tissue water (TDC) and Lymphedema Relative Volume (LRV) measured with WDM after 1,2,3 and 6 months standard treatment were examined. In paper III, (n=70), differences between compression group (CG) and non-compression group (NCG) in changes of local tissue water (TDC), LRV (WDM), and subjective symptoms after 1,2,3 and 6 months were investigated. Also, adherence to self-care at 6 months was examined. In paper IV, (n=51), difference between CG and NCG in disease specific HRQOL was investigated with the Lymphedema Quality of Life Inventory (LyQLI) at 6 months.

Results: The TDC method detected more patients with mild BCRL, earlier after surgery and at a lower LRV compared to the WDM method, but both methods together with skin palpation for diagnosis were needed. Also, there was a negative association between local tissue water and LRV (paper I). Both TDC and WDM could detect a significant reduction in BCRL over a 6 months period of standard treatment. The participants with BCRL, detected with TDC, decreased in local tissue water, but all participants had a similar decrease in LRV. Also, in a majority of participants, the site with the highest TDC ratio changed to another site (paper II). Early treatment with a compression garment for 6 months could prevent progression in mild BCRL, showing smaller proportions of progression in LRV, larger reduction in LRV and local tissue water, and early reduced experience of tension, compared to NCG. However, 43% in the NCG group did not show progression and could manage without compression. Adherence to self-care was comparable in both groups (paper III). The participants in both CG and NCG rated a high HRQOL, but the CG experienced a higher negative impact on HRQOL in the practical domain and in some of the items in the psychosocial domain compared to the NCG (paper IV).

Conclusions: TDC and WDM can be used together with skin palpation for early diagnosis. Both methods could detect changes in mild BCRL during treatment and can be used to evaluate treatment. Early treatment with compression garment for 6 months could prevent progression of mild BCRL, but almost half of the participants in the NCG did not show progression. Wearing a compression garment has a minor negative impact on HRQOL and needs to be considered in relation to the preventive effect. The results have important clinical implications for diagnosing, treatment, clinical decision making and patient education in women with mild BCRL.

Key words Diagnosis,compression garment, Health-Related Quality of Life,Tissue Dielectric Constant,Water Displacement Method,Breast Cancer-Related Lymphedema

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This thesis is dedicated to all women with breast cancer-related lymphedema. My hope is that it will improve diagnosis and treatment and thereby their Health-Related Quality of Life.

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Abstract

Background: Early diagnosis and treatment of Breast Cancer-Related Lymphedema (BCRL) are important to prevent lymphedema progress and impact on Health-Related Quality of Life (HRQOL). The treatment includes self-care and treatment with compression garment. In mild BCRL, the lymphedema can be local, without an increase in arm volume. Tissue Dielectric Constant (TDC), measuring local tissue water in skin and subcutis, had not been used for diagnosis and to evaluate treatment in mild BCRL before. Also, knowledge about the effect of wearing a compression garment and its impact on HRQOL was unknown. The overall aim of this thesis was to evaluate diagnostic methods, treatment, and HRQOL in women with mild BCRL.

Methods: Women treated with axillary node dissection and diagnosed with mild BCRL were included. In paper I (n=72), the proportion of mild BCRL detected with TDC and/or Water Displacement Method (WDM) in combination with skin palpation at diagnosis were evaluated. Also, association between TDC and WDM measurements and lymphedema related factors were examined. In paper II, (n= 46), changes in local tissue water (TDC) and Lymphedema Relative Volume (LRV) measured with WDM after 1,2,3 and 6 months standard treatment were examined. In paper III, (n=70), differences between compression group (CG) and non-compression group (NCG) in changes of local tissue water (TDC), LRV (WDM), and subjective symptoms after 1,2,3 and 6 months were investigated. Also, adherence to self-care at 6 months was examined. In paper IV, (n=51), difference between CG and NCG in disease specific HRQOL was investigated with the Lymphedema Quality of Life Inventory (LyQLI) at 6 months.

Results: The TDC method detected more patients with mild BCRL, earlier after surgery and at a lower LRV compared to the WDM method, but both methods together with skin palpation for diagnosis were needed. Also, there was a negative association between local tissue water and LRV (paper I). Both TDC and WDM could detect a significant reduction in BCRL over a 6 months period of standard treatment. The participants with BCRL, detected with TDC, decreased in local tissue water, but all participants had a similar decrease in LRV. Also, in a majority of participants, the site with the highest TDC ratio changed to another site (paper II). Early treatment with a compression garment for 6 months could prevent progression in mild BCRL, showing smaller proportion of progression in LRV, larger reduction in LRV and local tissue water, and early reduced experience of tension, compared to NCG. However, 43% in the NCG group did not show progression and could manage without compression. Adherence to self-care was comparable in both groups (paper III). The participants in both CG and NCG rated a high HRQOL, but the CG experienced a higher negative impact on HRQOL in the practical domain and in some of the items in the psychosocial domain compared to the NCG (paper IV).

Conclusions: TDC and WDM can be used together with skin palpation for early diagnosis. Both methods could detect changes in mild BCRL during treatment and can be used to evaluate treatment. Early treatment with compression garment for 6 months could prevent progression of mild BCRL, but almost half of the participants in the NCG did not show progression. Wearing a compression garment has a minor negative impact on HRQOL and needs to be considered in relation to the preventive effect. The results have important clinical implications for diagnosing, treatment, clinical decision making and patient education in women with mild BCRL.

List of papers

This thesis is based on following four papers:

I. Karlsson K, Nilsson-Wikmar L, Brogardh C, Johansson K. Palpation of Increased Skin and Subcutaneous Thickness, Tissue Dielectric Constant, and Water Displacement Method for Diagnosis of Early Mild Arm Lymphedema. Lymphat Res Biol. 2020 Jun;18(3):219-25. PubMed PMID: 31596662. Epub 2019/10/10.

II. Karlsson K, Johansson K, Nilsson-Wikmar L, Brogardh C. Tissue Dielectric Constant and Water Displacement Method Can Detect Changes of Mild Breast Cancer-Related Arm Lymphedema. Lymphat Res Biol. 2022 Jun;20(3):325-334. doi: 10.1089/lrb.2021.0010. Epub 2021 Sep

III. 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 Jul;61(7):897-905. DOI: 10.1080/0284186X.2022.2081932

IV. Blom KY, Johansson KI, Nilsson-Wikmar LB, Brogårdh CB. Health-Related Quality of Life in women with mild breast cancer-related lymphedema, 6 months after randomization to compression or not. Submitted.

Svensk sammanfattning

Bakgrund: Tidig diagnos och behandling av bröstcancer-relaterade lymfödem (BCRL) är viktigt för att förhindra försämring och påverkan på livskvalitet. Vid mindre BCRL i arm, kan det ansamlas lymfvätska lokalt i den ytliga vävnaden, utan en volymökning. Tissue Dielectric Constant (TDC), är en metod som mäter lokal vävnadsvätska i hud och subkutan vävnad och hade inte använts tidigare för att diagnostisera och utvärdera behandling av mindre armlymfödem. I behandlingen ingår bland annat användning av en kompressionsärm, men kunskapen om effekten och påverkan på livskvalitet saknades. Det övergripande syftet med avhandlingen var att utvärdera diagnostiska metoder, behandling och hälsorelaterad livskvalitet hos kvinnor med mindre BCRL.

Metod: Kvinnor som opererats med axillutrymning och diagnostiserats med mindre BCRL i arm inkluderades. I artikel I (72 deltagare), undersöktes andelen med mindre BCRL som upptäckts med TDC och/eller Pletysmografi/Water Displacement Method (WDM) i kombination med palpation av huden vid diagnos. Även faktorer relaterade till lymfödem och sambandet mellan lokal vävnadsvätska och relativ lymfödemvolym undersöktes. I artikel II (46 deltagare), undersöktes förändringar i lokal vävnadsvätska (TDC) och relativ lymfödemvolym (WDM) efter 1,2,3 och 6 månaders användning av en kompressionsärm. I artikel III (70 deltagare) jämfördes skillnader i förändring av lokal vävnadsvätska (TDC), relativ lymfödemvolym (WDM), och subjektiva symtom efter 1,2,3 och 6 månader, mellan de som använt och inte använt kompressionsärm. Även frekvens av egenvård vid 6 mån undersöktes. I artikel IV (51 deltagare), undersöktes skillnader i upplevd hälso-relaterad livskvalitet mellan de som använt och inte använt kompressionsärm under 6 månader.

Resultat: TDC-metoden kunde upptäcka fler patienter med mindre BCRL, tidigare efter operationen och vid en lägre lymfödemvolym jämfört med WDM, men båda metoderna tillsammans med palpation av huden behöver användas vid diagnostisering. Det fanns ett samband mellan ansamling av lokal vävnadsvätska (TDC) och relativ lymfödemvolym (WDM) (artikel I). Både TDC och WDM kan mäta förändringar av BCRL under behandling och kan användas vid utvärdering av behandling. De deltagare med BCRL som upptäckts med TDC metoden minskade i lokal vävnadsvätska, men alla deltagare minskade i relativ lymfödemvolym. Det högsta TDC värdet förflyttades i en majoritet av fallen till en annan mätpunkt under interventionen (artikel II). Tidig behandling med kompressionsärm under 6 månader kunde förhindra försämring av mindre armlymfödem, då den minskade relativ lymfödemvolym, lokal vävnadsvätska och minskade upplevelsen av spänning i armen, jämfört med deltagare som inte använt kompressionsärm. Emellertid, så var det 43% av de som inte använde kompressionsärm som inte försämrades i relativ lymfödemvolym och kunde klara sig utan behandling med kompressionsärm. Det var ingen skillnad i frekvens av egenvård mellan grupperna (artikel III).

Deltagarna med mindre BCRL i båda grupperna skattade en hög hälsorelaterad livskvalitet, men de som använde kompressionsärm upplevde mer negativ påverkan på hälsorelaterad livskvalitet i den praktiska domänen och i några psykosociala aspekter jämfört med de som inte använt kompressionsärm (artikel IV).

Slutsatser: TDC och WDM kan användas tillsammans med palpation av huden för att diagnostisera tidiga mindre BCRL. Båda metoderna kan mäta förändring under behandling och kan användas vid utvärdering av behandling. Tidig behandling med kompressionsärm under 6 månader förhindrar försämring av mindre BCRL, men nästan hälften av de deltagare som inte använt kompressionsärm försämrades inte. Att använda kompressionsärm har en mindre negativ påverkan på upplevd hälsorelaterad livskvalitet och behöver beaktas i relation till den preventiva effekten av att använda kompressionsärm. Resultaten i avhandlingen har viktiga kliniska implikationer för diagnostik, behandling och patientutbildning hos kvinnor med mindre BCRL.

Abbreviations

ALND	Axillary Lymph Node Dissection
BCRL	Breast Cancer-Related Lymphedema
BIS	Bioimpedance Spectroscopy
BMI	Body Mass Index
CDT	Complex Decongestive Therapy
CG	Compression Group
HRQOL	Health-Related Quality of Life
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Functioning, Disability, and Health
LRV	Lymphedema Relative Volume
LyQLI	Lymphedema Quality of Life Inventory
MDC	Minimal Detectable Change
MLD	Manual Lymph Drainage
NCG	Non-Compression Group
RCT	Randomized Controlled Trial
RT	Radiation Therapy
SEM	Standard Error of Measurements
SLD	Simple Lymphatic Drainage/Self Lymphatic Drainage
SLNB	Sentinel Lymph Node Biopsy
TDC	Tissue Dielectric Constant
VAS	Visual Analogue Scale
WDM	Water Displacement Method

Thesis at a glance

Paper	Aims	Methods	Results	Conclusions
I	To evaluate TDC and WDM in combination with palpation for early diagnosis of mild BCRL, examine the association between TDC and WDM measurements and compare lymphedema related factors between groups diagnosed by these methods.	72 women with mild BCRL. Clinical examinations including measurements of local tissue water (TDC) and arm volume (WDM) at diagnosis.	Both TDC and WDM together with palpation could be used to diagnose early mild BCRL. The TDC method was the most valid method, detected earlier after surgery and at a lower lymphedema relative volume than the WDM. Local tissue water (TDC) and lymphedema relative volume (WDM) were negatively associated.	TDC and WDM can be used together with skin palpation for diagnosis of mild BCRL.
II	To examine if TDC and WDM can measure changes in mild BCRL over a 6 month period of standard treatment. Also, to examine changes within and between three groups based on lymphedema thresholds of TDC and WDM at start of treatment, as well as changes of the highest TDC value and site.	46 women with mild BCRL, treated with a compression garment for 6 months. Clinical examinations including measurements of local tissue water (TDC) and arm volume (WDM) at baseline and after 1,2,3 and 6 months	Both TDC and WDM could detect a significant reduction in BCRL. There was a significant difference between the defined groups in change of TDC ratio, but not in lymphedema relative volume. The majority of the highest TDC ratios changed to another site during the intervention.	Both TDC and WDM can detect changes in mild BCRL but should be interpreted separately.
III	To investigate the proportion of women with mild BCRL showing progression/no progression in lymphedema after treatment with or without a compression garment and differences in changes of lymphedema relative volume, local tissue water and subjective symptoms during six months. Adherence to the self-care regime was also examined.	70 women with mild BCRL treated with a compression garment or not for 6 months. Clinical examinations including measurements of local tissue water (TDC), arm volume (WDM) and rating of subjective symptoms (VAS) at baseline and at 1,2,3 and 6 months. Rating of adherence to self-care at 6 months.	Immediate treatment with a compression garment could prevent progression in mild BCRL, showing smaller proportions of progression, larger reduction in lymphedema relative volume and local tissue water, and reduced experience of tension, compared to no treatment with compression garment. Adherence to self-care was comparable in both groups.	Immediate treatment with a compression garment can prevent progression in mild BCRL.
IV	To investigate if there is a difference in disease specific HRQOL, between women with mild BCRL wearing compression garment or not for 6 months.	51 women with mild BCRL, rated their HRQOL after wearing compression garment or not for 6 months.	The compression group experienced a greater negative impact on HRQOL in the practical domain and in some of the psychosocial items, compared to the non-compression group.	The minor negative impact on HRQOL, when using a compression garment needs to be considered in relation to the preventive effect.

Preface

I have worked as physiotherapist in cancer rehabilitation for more than 20 years and since 2004 also as a lymphedema therapist. What has attracted me to work as a lymph therapist is that the individual response to different treatments is often variable and unpredictable, and therefore it is a great challenge to meet the specific needs of each patient. I have always been a reflective and curious clinician. In 2009, I began the master's program in clinical medical science, which included two studies that formed the basis of the issues in the doctoral thesis. In my work, I had asked myself the question of what happened to the patients with lymphedema who did not return for follow-up visits. I wondered if these patients were dissatisfied with the treatment or if they felt that they did not need any more treatment. In the first study included int the master's program we found that many of the women who chose to end their treatment had their lymphedema stabilized or in regression. In the second study I interviewed women with Breast Cancer-Related Lymphedema (BCRL). Results showed different ways of perceiving treatment and gave me a deeper understanding of individual variations in managing the lymphedema. During the master's program, Lena Nilsson-Wikmar was my main supervisor and she encouraged med to publish the two studies. After completing my master's degree, I discussed with Karin Johansson at Lund University Hospital. We were both curios about how many women with early BCRL who had no progression of their arm lymphedema, without treatment. Also, from previous studies and the clinic, we knew that some patients have problems using a compression garment and did not want to use compression. Therefore, it would be of interest to know how many would not need to use compression. During the same time, Karin Johansson had started using the Tissue Dielectric Constant (TDC) that could measure superficial fluid in the tissue. In a previous study she had found that the TDC had a potential and could be useful when diagnosing mild BCRL. Thoughts of a larger study began to take shape and Karin wanted to include me and another colleague to be able to perform measurements at Karolinska University Hospital in Stockholm. Karin Johansson submitted an ethics application for the project on early BCRL and the data collection started 2014. Thereafter Karin Johansson asked me if I could consider starting a licentiate student education, based on the planned studies on BCRL. At first, I was very hesitant about this, but Karin managed to persuade me and today I am very happy for that. A big reason why I started my doctoral studies was that I was very anxious to seek answers to the clinical questions that arose at the clinic, and I also thought that the results would be of great benefit to the patients. I have always seen myself as a researcher close to the clinic and think that it is very important that research results are useful and implemented in the clinic. For that reason, I have put a lot of research time into lecturing about the studies nationally and internationally. My time as a doctoral student has been very developing and inspiring and has made me a better clinician and researcher.

Introduction

Breast cancer is the most common form of cancer in women in Sweden and globally. Women who have undergone surgical or radiation treatment for breast cancer are at risk of developing lymphedema, which can cause swelling in the arm, hand, breast, or chest wall. The routine use of sentinel lymph node biopsy (SLNB) rather than axillary lymph node dissection (ALND) has resulted in a decreased incidence of Breast Cancer-Related Lymphedema (BCRL). However, the prevalence of lymphedema has increased as more effective oncologic therapies have improved patient survival. Having a lymphedema may result in physical, psychological, and social consequences, which can negatively impact a woman's health-related quality of life (HRQOL).

Early diagnosis and treatment including prescription of a compression garment and education/counselling in self-care may therefore be important to prevent lymphedema progress and decrease its negative impact on HRQOL. Care can be organized according to a pyramid based on the patients need for treatment, which depends on stage and origin of lymphedema (Figure 1). Basic needs include diagnosis and initial treatment and are often performed by lymphedema therapists working in hospitals which have breast cancer surgery and cancer rehabilitation. The cancer rehabilitation is based on interdisciplinary collaboration and treatments based on evidence. Also important, are the individualization of the patient's care according to their unique needs and values, active patient participation in treatment and patient empowerment. Special needs and care in the maintenance phase can in most cases be provided in the primary care. Advanced needs and highly complex care are provided in specialized lymphedema rehabilitation centers, in hospitals or in palliative care units. The studies included in this thesis are related to the first level, basic needs, according to the model of Cancer rehabilitation.

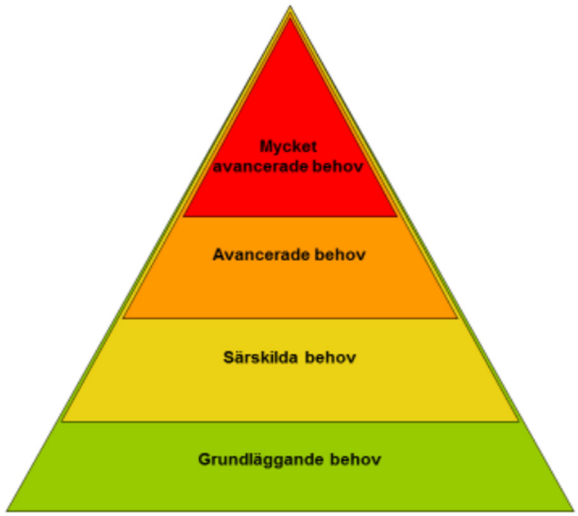

Figure 1. Cancer rehabilitation levels based on the patient's needs (basic, special, advanced and very advanced needs). From National program Cancer rehabilitation, with permission.

The lymphatic system

The main roles of the lymphatic system are to maintain fluid homeostasis, regulate inflammatory responses and enable dietary absorption of fat (1). It consists of lymphatic organs such as the thymus, spleen, and lymph nodes, but there is also lymphatic tissue in the gastrointestinal mucosa and in the mucous membranes of the respiratory tract. There are about 500-1000 lymph nodes in the body. These lymph nodes can occur both as individual lymph nodes or in groups near large blood vessels, for example in the armpits and groin. The main task of the lymph nodes is to produce B and T lymphocytes which can break down bacteria and foreign substances in the body (2).

The lymphatic system runs in parallel with the blood system. In the subcutaneous tissue, blood capillaries and the initial lymphatic vessels meet in a network, and between these are the interstitial spaces, which consist of water, protein molecules, fat, connective tissue, and long carbohydrate molecules. The pressure in the blood capillaries pushes water through the vessel wall. Lymph fluid is taken up by the pre-lymphatic ducts, which are then passed on to the lymph capillaries and on to pre-collectors and collectors (Figure 2). The lymph collectors consist of smooth muscle in the vessel wall (called lymphangioma), that interacts with valves that open in the direction of the heart. Functionally, the lymphatic system can be divided into the superficial system (subcutaneous) that drains the cutis and subcutis and the deep system that drains muscles, joints, tendons, nerves and the body's organs (2).

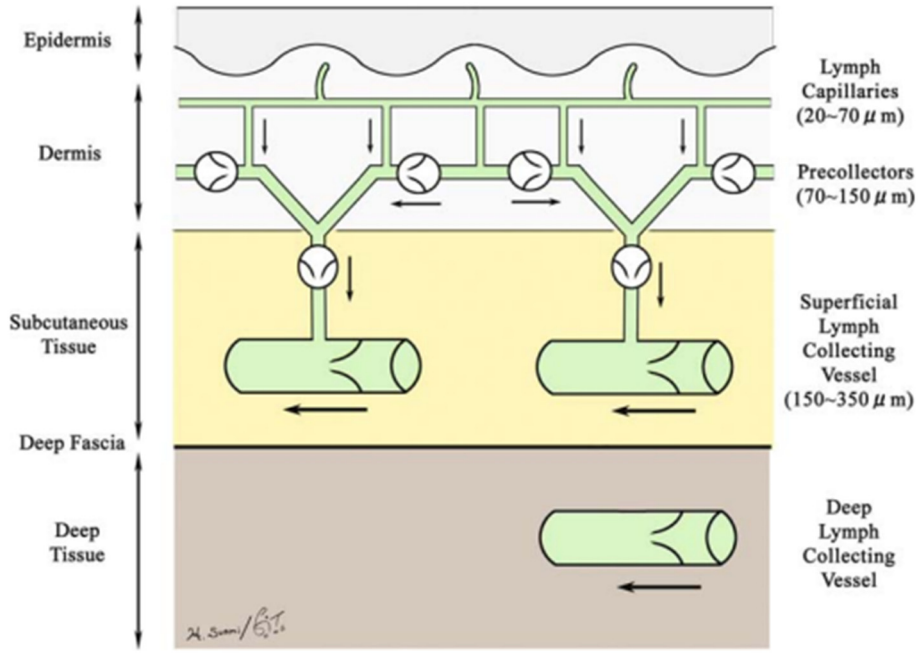

Figure 2. Schematic diagram of the relationship between the lymph capillaries,precollectors and lymph collecting vessels. With permission from Hiroo Suami (3).

In the upper extremity, the superficial lymphatic system is divided into an ulnar bundle and a radial bundle. The ulnar bundle drains the medial arm and follows the basilic vein to the axillary lymph nodes. The radial bundle obtains lymph from the lateral arm and accompanies the cephalic vein to the axillary lymph nodes of the pectoralis major muscle. The lymph fluid normally drains to either the supraclavicular and/or infraclavicular lymph nodes and to the thoracic duct (left side) or lymphatic duct (right side) and thereafter back to the cardiovascular system (1).

Breast cancer and side effects of treatment

Breast cancer is the most common form of cancer in women in Sweden and globally. Approximately 8000 women per year are diagnosed with breast cancer in Sweden (4). As diagnostic methods and treatment for breast cancer have improved, the 5-year survival rate has improved and is currently approximately 90% (5). The cause of breast cancer is not completely clear, but hormonal factors, lifestyle and hereditary predispositions are considered to increase the risk (5).

The standard treatment for most breast cancer consists of surgery and radiation therapy (RT). Also, additional treatment with chemotherapy (based on Taxanes, Anthracyklines, Capecitabine), hormonal treatment or monoclonal antibodies may be needed to improve survival (5).

Today, SLNB is routine as a staging method of the axillary lymph nodes for patients with clinically free axilla. The SLNB technique has been evaluated in several studies that have shown decreased risk of arm symptoms, low incidence of axillary relapse and a comparable survival (5). ALND is performed in approximately 20-30% of all patients with more than two verified axillary macro-metastases, or sometimes if there is metastasis in the sentinel node after preoperative treatment (5). The surgery with ALND is usually performed up to level I- II of lymph nodes, which involves about 10-20 lymph nodes located between the axillary vein, the thoracodorsal bundle, and the long thoracic nerve (5, 6).

In metastasis to the axilla and surgery with ALND, RT is given locoregional to the breast, lymph nodes in fossa supraclavicular and sometimes also to parasternal lymph nodes. In some cases, especially in younger patients, an extra dose (Boost) is given to the tumor area (5). The RT can cause injury to plexus brachialis, which can cause numbness in the arm (7), pneumonitis and fibrosis (8). The fibrosis can cause compression of lymphatic vessels, which decreases the function of the lymphatic system (9).

Patients who have been treated for breast cancer may develop treatment related side-effects. It is common with weight gain and menopausal symptoms from hormonal treatment (10). Also, cognitive dysfunction (11, 12) and physical symptoms such as breast/arm pain, fatigue, reduced range of motion, weakness in the upper limb and lymphedema are common (13).

Lymphedema

Lymphedema is defined as swelling due to accumulation of interstitial tissue fluid in a body part. When the lymphatic system fails to transport the lymph produced by a body part, congestion results. The solid and fluid constituents of lymph accumulate in the interstitial space and results in stasis of protein rich interstitial fluid and chronic inflammation (1, 14).

Lymphedema may be described as primary or secondary based on its presumed etiology. Approximately 99% of patients with lymphedema have secondary disease and primary lymphedema is rare (1). Primary lymphedema (congenital) relates to intrinsic factors such as genetic predisposition that can lead to the malformation of lymphatic vessels.

Secondary lymphedema often arises from external effects to the lymphatic system, for example surgery or radiation therapy, but it may also arise from internal causes such as infection, traumatic injury, cancer disease and inflammation (1). The traditional division of lymphedema into primary lymphedema or secondary lymphedema, is nowadays discussed. The term "latent lymphedema", defined as an inherited critical balance between lymph fluid production and transport, and "constitutional lymphedema" defined as constitutional lymphatic weakness can be used as a complement to the terms secondary and primary lymphedema (15).

Breast cancer-related lymphedema (BCRL)

Pathophysiology

The accumulation of lymph fluid is mainly epifaschial and referred to as dermal backflow in the tissue. Dermal backflow is caused by dilated dermal lymphatic capillaries and pre-collectors and develops when there is an obstruction of the superficial lymph-collecting vessels, for example due to fibrosis. The lymph fluid is transported through alternative pathways to functioning lymph-collectors (16). The degree of dermal backflow has shown to correlate with the severity of lymphedema (17). Stanton et al (18) found that the subfascial lymph drainage too is impaired. They found a correlation between impairment of subfascial drainage and epifascial arm swelling. This may be due to the severity of axillary damage, and that the loss of function in subfascial lymphatics impairs drainage from the epifascial to the subfascial system

The aetiology of BCRL is poorly understood and multifactorial. BCRL has been found not to develop at once in the entire arm, and sometimes, the hand is spared from lymphedema. The hypothesis is that regional differences in surviving lymphatic function contribute to the distribution of swelling (16, 17, 19), (Figure 3). Koelmeyer et al (20) found that the ipsilateral axilla was the most frequent compensatory drainage region (74.9%), followed by clavicular (41.8%) and parasternal (11.3%) after surgery with ALND.

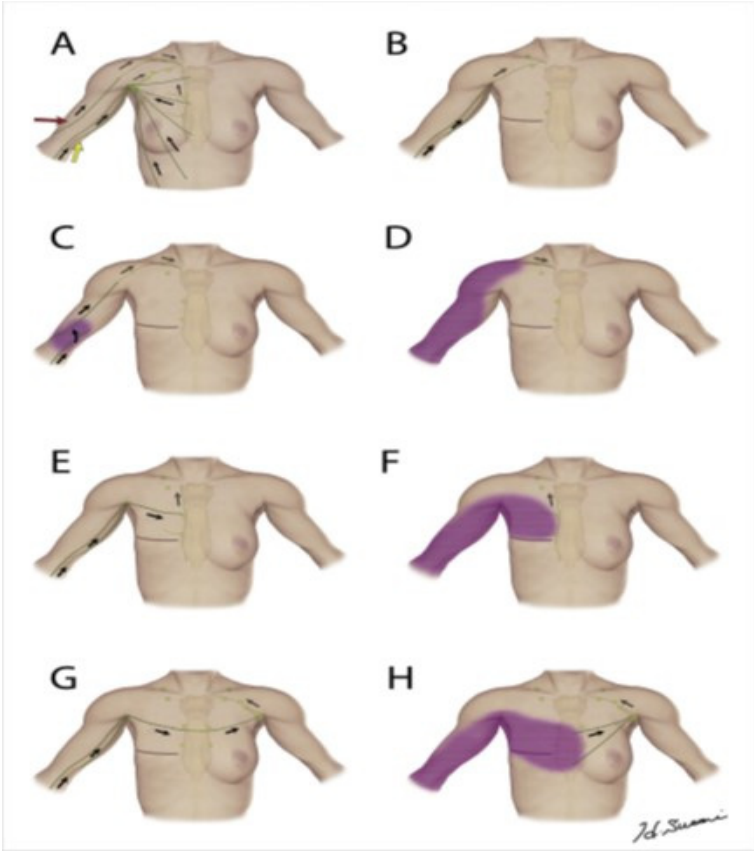

Figure 3. Schematic diagram in the forequarter representing the lymphatic pathway variation from the upper extremity after axillary node dissection as summarised from the reviewed data. Flow direction is indicated in black. The normal lymphatics in the upper limb drain to the supraclavicular lymph nodes (red) and the axillary lymph nodes (yellow) as a control (A). The drainage pathways are to the ipsilateral axillary (B), supraclavicular (C,D), internal mammary (E,F), and contralateral axillary nodes (G,H). Lymph fluid could be carried by regenerated lymphatic vessels (B,E,G), the lateral pathway (C) or dermal backflow (D,F,H). Reprinted from (19). Copyright (2018) with permisssion from Elsevier.

Axillary reverse mapping (ARM) has been performed to prevent lymphedema during ALND by visualizing the upper extremity lymphatics, and cranial collectors have been found to be a negative predictor of lymphedema (21). Stanton et al (22), also found that women with higher filtration rates, and therefore higher lymph flows through the axilla, are at greater risk of BCRL, and concluded that some women have a defined, constitutive predisposition to secondary lymphedema. Venous outflow may also be comprised in lymphedema leading to increased fluid filtration and higher load on the lymphatic system (23, 24).

Risk factors

One of the crucial issues in lymphedema is that we cannot predict which patients will suffer from the ailment in the future and which will be spared. Lymphedema can develop at any time after completion of cancer treatment (25). Risk factors for BCRL with strong evidence mentioned in the literature are surgery with ALND and a larger number of lymph nodes removed (>5 lymph nodes), (26), surgery with mastectomy and overweight (Body Mass Index (BMI) >30 kg/m^2) (27, 28). Other risk factors with moderate evidence are oncological treatment with radiotherapy to regional lymph nodes, chemotherapy, number of metastatic lymph nodes, and a sedentary lifestyle (27, 28). Also, cellulitis is a well-established BCRL risk factor in the literature (28).

Incidence

The incidence of BCRL varies depending on follow-up time and the diagnostic method and threshold used. In prospective cohort studies the incidence varies between 14.9-29.8% (27). The routine use of SLNB rather than ALND has resulted in a decreased incidence of BCRL, with rates of 34.8 % associated with ALND compared to 4.6 % for SLNB (29). In a Swedish cohort of 292 women with BCRL, treated with ALND and radiotherapy, the incidence was 38.7% (30). Similar results have been reported by others (31, 32). Norman et al (33) used a questionnaire where women with BCRL self-reported degree of lymphedema and they found an incidence of 42% within 5 years after surgery. Of these, 80% were diagnosed within 2 years, and 89% within 3 years. There are only a few studies with long term follow up. Petrek et al (34) examined prevalence of BCRL and associated predictive factors 20 years after diagnosis. The women reported circumferential arm measurements taken and the prevalence was found to be 49%.

Progression/regression

Lymphedema can progress without appropriate treatment. With time, the protein in the lymph fluid can damage the tissue through chronic inflammation and stimulating the formation of new connective tissue and can render it hard and fibrotic. There may also be a growth of the subcutaneous fat and gradually there may be a transformation into adipose tissue, without pitting in the tissue (35). These pathological changes over time usually lead to a chronic disease (1) and without treatment, progression can be expected (36). Bar Ad et al (37) found that the rate of freedom from progression to more severe lymphedema was 79% at 1 year, 66% at 3 years, and 52% at 5 years.

The severity of the lymphedema can be graded according ISL to stages (0-3), based on clinical findings and/or based on lymphedema relative volume (38). Minimal BCRL corresponds to a LRV 5-20%, moderate (LRV 20-40%) and severe to (LRV >40%). However, some prefer to use LRV 5-10% as minimal and 10%-20% as mild lymphedema (38). In Sweden, severe lymphedema (LRV>40%) is quite rare. Therefore, LRV 5-10% is considered as mild lymphedema and LRV 10-20% as moderate lymphedema.

Although most lymphedema is expected to progress without treatment, some cases of early mild BCRL may be reversible or remain stable over many years (30, 39). Regression of BCRL has also been noted by others. Kilgore et al (32) found that 82% of the women with BCRL, who had elevated Bioimpedance Spectroscopy (BIS) measurements, returned to normal baseline range, and only 6% had persistent BCRL requiring referral for advanced therapy. Patients with persistent BCRL had significant nodal burden on surgical pathology.

Early detection and diagnosis of BCRL

Early diagnosis and treatment of BCRL is recommended to prevent progression (40), and augments the chance of a disease cure (17). Traditionally, the detection of BCRL has been based on several methods such as arm volume measurements using Water Displacement Method (WDM) or circumferential measurements with a tape measure, and the use of patient surveys. The diagnosis is complicated due to a lack of consensus on valid and reliable measurement methods, and varying diagnostic threshold values. Commonly used thresholds are >10% Lymphedema Relative Volume (LRV) or >2 cm difference in circumference between the arms (27). However, there is an increased risk of underestimating and missing an early mild BCRL using these thresholds for detection of mild BCRL. Several authors recommend that patients should be screened for lymphedema at a low lymphedema volume, because a larger lymphedema volume at diagnosis and early onset are known risk factors for progression.

Stout-Gergerich et al (41), defined a 3% volume change from a preoperative baseline as a diagnostic criterion for subclinical lymphedema. Specht et al (42), suggested a threshold of LRV >5 % to <10 % change compared to preoperative arm volume, for close monitoring or intervention. This limit was significantly associated with an increased risk of LRV exceeding 10%, especially if the LRV had changed 3% to 5% within 3 months of surgery. Moreover, an increase in LRV >5 % within one month after surgery was associated with a 40% increased risk of lymphedema (43). The National Lymphedema Framework recommend a threshold of LRV ≥5% for early intervention (44).

Along with volume measurements, clinical examination of the skin, with attention to the colour and decreased visibility of subcutaneous veins (Figure 4), palpation of increased skin and subcutaneous tissue and pitting are also important diagnostic signs (45).

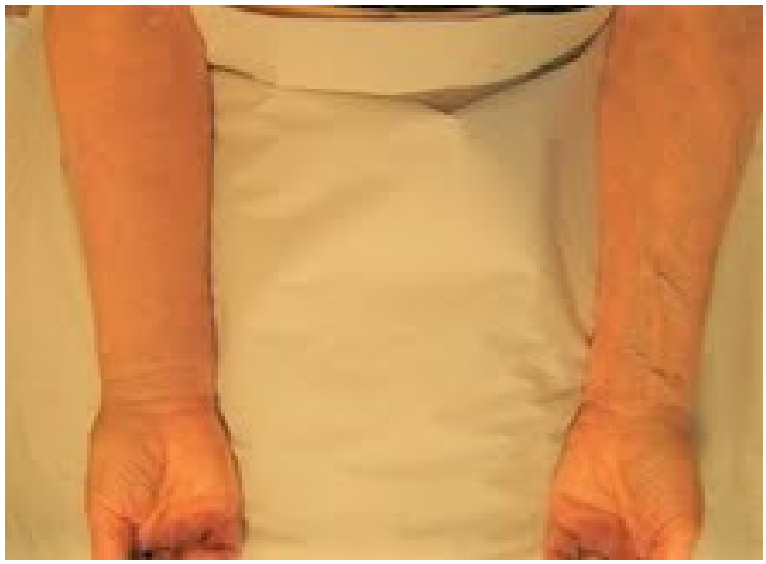

Figure 4. Decreased visibility of subcutaneous veins in right arm.© by Karin Johansson

In Sweden, palpation of skin and increased thickness in subcutis together with volume measurements have been used as standard methods in the clinics for diagnosis of BCRL (30). Skin thickness has been shown to correlate with the degree of swelling (46) and dermal backflow (47). However, due to small LRV in mild BCRL, variation of arm volume in the dominant and nondominant arm (48) and in the absence of preoperative arm volume measurements, volume measurements may not be sensitive enough to detect an early mild BCRL (49, 50).

There are new diagnostic methods that have improved sensitivity over more traditional methods such as volume measurements and lymphoscintigraphy, and a selection of some of these methods is presented in (Table 1).

Table 1. Selection of some diagnostic methods for detecting early BCRL.

Method	Measures
Indocyanide green lymphography/ Near-infrared Flourescence	Imaging technique. Patterns in dermal backflow (51) (17, 47, 52).
Bioimpedance spectroscopy (BIS)	Extracellular fluid (53-56).
Tissue Dielectric Constant (TDC)	Local tissue water (57, 58).
Dual-energy X-ray absorptiometry	Tissue composition (59).
Subcutaneous echogenicity grade (SEG)	Ultrasonographic scanning of skin and subcutaneous thickness (60).

However, some of these methods are not useful in the clinic because they require specialised equipment or skills and are time-consuming or expensive. Instead, Tissue Dielectric Constant (TDC) can be used to identify local tissue water in skin and upper subcutis and is easy to perform. Only one measurement is required (61) and there is no need to have preoperative values (62). Lahtinen et al (58) compared TDC with BIS and found a significant higher sensitivity for the TDC (65.8%/42.1%) respectively. They concluded that the discrepancies between TDC and BIS techniques were related to different techniques and the assessed anatomical regions. The results supported the role of TDC as a method for early detection of lymphedema. Mazor et al (49) used TDC and examined women with BCRL and found a significant difference between the affected and non-affected side for the trunk, upper arm, and forearm. Also, Bakar et al (63) measured with TDC, and compared patients with BCRL with women without BCRL and found a significant difference between groups. At the time of planning the studies included in the thesis, studies evaluating the TDC and WDM method for detection of mild BCRL, were lacking.

Consequences of BCRL

A framework that can be used to describe the consequences of BCRL is the International Classification of Functioning, Disability and Health (ICF) (64). The ICF covers aspects of impairments, activity limitations and participation restrictions, as well as personal and environmental factors (64). BCRL can cause physical impairments such as a heavy, stiff, and swollen arm, but also emotional reactions such as feelings of sadness, discourage or stress. These impairments may result in activity limitation and participation restrictions (65, 66). A severe stage of lymphedema in the arm can make activities of daily living difficult, for example taking care of children, carrying, or lifting heavy objects, yard work or gardening, or house cleaning (67), and therefore have a negative impact on HRQOL (68).

Health-Related Quality of Life in women with BCRL

The term HRQOL refers to the health aspects of quality of life, and is generally considered to reflect the impact of disease and treatment on disability and daily functioning (69). HRQOL can be described as “how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health” (70). BCRL is associated with lower levels of HRQOL and with physical, psychological, and social consequences compared to breast cancer patients without lymphedema (68, 71). Physical functions in patients with BCRL have shown to have a higher impact on HRQOL than psychological or social aspects (72).

Among common arm symptoms, pain in the affected arm has shown to correlate more with poor HRQOL outcomes, than the arm volume (73-75).

Psychological impact reported are perceptions related to body image as appearance, sexuality, and social barriers (76). Negative emotions experienced are anxiety, frustration, sadness, anger, fear, and increased self-consciousness (77). Also, women with BCRL may have decreased self-confidence resulting from a distorted body image (68). Other important predictors of low HRQOL in women with BCRL are younger age, a high body weight (68) but also a lower education level and family income (78).

Some qualitative studies indicate that wearing a compression garment may affect HRQOL. In an interview study of women with BCRL, receiving lymphedema treatment, it turned out that some women stopped using the compression garment on their own initiative, related to problems with the compression garment (79). Also, Johansson et al (80) interviewed women with mild or moderate BCRL and reported that some women experienced that the compression garment did not work well or that it irritated. The garment attracted attention and was experienced as ugly, terrible, un-feminine and warm. At the time of planning the studies, knowledge of the impact on HRQOL of wearing a compression garment was lacking.

Treatment of BCRL

The treatment consists of several different components, of which compression and self-care is the most important. The overall goal of the treatment is to reduce the lymphedema volume and decrease subjective symptoms in the affected arm and/or breast, thus decrease its impact on activities, participation in society and HRQOL. However, equally important, in the role as physiotherapist is to assess cancer rehabilitation needs according to the ICF and treat other symptoms as pain, fatigue, decreased strength, reduced range of motion or hot flashes. It is also important to have a holistic perspective, such as to help the patient to obtain psychosocial support or to receive help from dietitian if necessary.

Standard treatment

In Sweden, a follow-up including information/education about lymphedema and examination of patients treated with ALND is now recommended (81). The education includes anatomy, physiology, risk factors for developing lymphedema and information on how and when to act if they identify symptoms of BCRL to enable early diagnosis and treatment.

Breast cancer patients who have received information about lymphedema have shown to have significantly reduced symptoms, increased knowledge about BCRL (82), and increased compliance and activity level (83).

The standard treatment of mild BCRL, includes prescription of a compression arm sleeve and education/counselling in self-care including exercise, weight control, skin care and self-massage (84, 85). In the early stage, a compression garment can reduce the lymphedema volume (30, 41) and is recommended (84). In a few cases, if there is still progression of arm lymphedema, more individualized treatment like bandaging (84, 86) or custom-made compression sleeves with adjusted pressure may be necessary to reduce the lymphedema volume.

Compression

Compression treatment is found to be the most important component in lymphedema treatment, at any stage of severity (87). Compression reduces lymphedema volume by reducing capillary fluid filtration, increases lymphatic drainage, moves fluid to non-compressed areas, decreases fibrosclerotic tissue, improves venous pump action and increases microcirculatory blood flow velocity (88). The lymphatic drainage is improved by increasing tissue pressure providing a counterforce to muscle contractions and so improving the muscle pump (89). Compression also helps to support the tissues and maintain the shape of the extremity (90), reduces proinflammatory cytokines and rise in anti-inflammatory mediators in the compressed tissue which improves the skin condition (91).

The garment pressure is measured in mmHg and divided into different compression classes. In Sweden the German standard of compression classes is used, Compression class (ccl) 1 corresponds to 18-21 mmHg, ccl 2: 23-33 mmHg, ccl 3:34-46 mmHg and ccl 4:>49 mmHg (92). The garments can be either round-knitted or flat-knitted. The material and compression class used are individually adjusted depending on the severity of the lymphedema (92). In early mild BCRL a ccl 1 compression garment can be used (92). In the studies included in the thesis, most of the participants were treatment with a round-knitted ccl 1 compression garment (Figure 5). It is crucial that the compression garments are effective and acceptable by the patients, as the lymphedema is likely to re-accumulate spontaneously if compression garment is not worn.

Vignes et al (93) showed that non-compliance to low stretch bandage and elastic sleeve were risk factors for an increased lymphedema volume after 1-year of maintenance treatment. In recent years, new compression such as adjustable compression with Velcro and night compression (94) can be used as complement to compression garment. This makes it possible to individually adjust the compression and improve adherence to treatment.

Figure 5. Round-knitted compression sleeve. © Katarina Blom

Early intervention with compression garment

Early intervention is recommended (44), and is based on studies that have examined the effect of early intervention with patients participating in a monitoring or surveillance program with several interventions, including the wearing of a compression garment (40). Soran et al (95) followed 186 women treated with ALND, and the incidence of clinical lymphedema was reduced with 36.4% compared to 4.4% in the control group. Also, Yang et al (96) followed 707 women and found that the overall 5-year cumulative incidence of lymphedema decreased from 48% to 25%. Although early diagnosis and treatment of BCRL are recommended (44) there is a lack of knowledge about the proportion of women who do not progress in lymphedema. Also, very few studies have assessed the effect of compression garments in women with BCRL (97). Stout-Gergich et al (41) evaluated treatment with a compression arm sleeve in early BCRL, for 4 weeks and found a mean LRV decrease of -2.4%, on average 4.6 months from start of intervention. In another study by Johansson & Branje (30), on early diagnosis with a LRV, ≥5%, it was shown that 27% still had a LRV ≤5%, mean 5 years after diagnosis. However, it was unclear if the maintenance of the low level of LRV, was due to the treatment with compression garment or if the lymphedema had otherwise stabilized at a low level. Also, in a retrospective study, comparing patients who had continued treatment with these who had discontinued treatment, the results showed no difference in progression/regression, indicating that there may have been a spontaneous regression among the patients who discontinued treatment (39).

At the time of planning the studies included in the present thesis, there was a need for more randomized trials examining the effect of wearing compression garment in women with mild BCRL.

Self-care

Self-care includes education/counselling about exercise, weight control, skin care and self-massage (84, 86). Effective lymphedema self-care is important to reduce the impact of lymphedema on well-being, and to minimize complications and disease progression. However, little is known about the effectiveness of the self-care (98). Lymphedema self-care helps to maintain symptom control but may also be experienced as burdensome (99). Ridner et al (99) found that those with more symptoms spent more time on self-care activities and had a poorer quality of life. Brown et al (100) examined adherence to self-care modalities and found that the average adherence to self-care was non-optimal. Research in Self-Regulation Theory suggests that objective self-measurement of physiological conditions is necessary to promote self-regulation/self-care (101). Ridner et al (102) used BIS for self-measuring and found a better adherence to self-care.

Exercise

Physical activity/exercise is an important component in the treatment of breast cancer. In a holistic perspective, it reduces side effects of cancer treatment, but also the risk of recurrence (103). Exercise is also important to maintain strength, function, normal weight and HRQOL. Earlier, it was thought that exercise could develop or worsen a lymphedema. Nowadays, there is evidence that resistance training will not worsen a lymphedema (104) and may even prevent arm lymphedema in breast cancer (105). In another systematic review with meta-analysis, a significant reduced risk was found in the exercise groups compared to no exercise, but only for the patients who had surgery with ALND (106).

Weight control

Overweight (BMI >30 kg/m^2) is a strong risk factor for BCRL (27, 28) and therefore overweight women are advised to maintain a healthy weight to improve the outcomes of previously diagnosed BCRL (107). However, the effect of weight-loss on BCRL is unclear. Schmitz et al (108) found that weight loss, home-based exercise, and combined interventions did not improve BCRL outcomes in overweight breast cancer survivors.

Skincare

Preventative information for lymphedema includes information to keep skin and nails clean and cared for to prevent infection and avoid skin trauma (109). The recommendations are to use cream or lotion to keep the skin moist and to clean small cuts or breaks in the skin. Also, to pay extra attention to redness around wounds and in case of signs of infection, seek help from a doctor to receive antibiotic treatment. Concerning blood drawing and acupuncture in the limb at risk of lymphedema one may do so without increased risk of getting an infection or developing lymphedema (110, 111). However, if one has a lymphedema, it is preferable to use the healthy arm, if possible, but the benefit is to be weighed against the possible risk of infection.

Self-massage

Self-massage is a modified treatment of the simple lymphatic drainage/self-lymphatic drainage (SLD), based on the massage technique Manual Lymph Drainage (MLD). However, in several systematic reviews with meta-analysis it has been concluded that it does not reduce the lymphedema (87, 112, 113), neither does it prevent the risk of lymphedema (113). Further, the minor effect of MLD in subgroups needs to be considered both against the time it takes to perform the treatment and the cost (114). The self-massage taught to the participants included in the studies, comprised instructions on light strokes over the shoulder and arm in a proximal direction for about 10-15 minutes a day. The current literature is limited on the effectiveness of SLD compared to no SLD in decreasing arm volume (115). Therefore, the main purpose of the self-massage is to reduce symptoms such as heaviness and tension in the arm, based on the theory that touching the skin can release hormones such as oxytocin and endorphins which may reduce symptoms. However, even if the self-massage is harmless, the treatment effect needs to be evaluated regularly so as not to place an unnecessary element of stress on the patient.

Methods for evaluating treatment

Measuring the lymphedema volume

The effectiveness of treatment is traditionally evaluated by measuring either volume with WDM or measuring the circumference and calculate the volume (116). However, in mild BCRL the accumulation of lymph fluid can be local, without increase in arm volume. Also, WDM may not be sensitive enough to measure changes in mild BCRL, due to inherent volume differences in the dominant and non-dominant arm (48) and in the absence of preoperative arm volume measurements.

TDC measuring local tissue water in skin and subcutis, can be applied to identify local lymphedema changes (58), but only a few studies have evaluated lymphedema treatment with TDC. Tugral et al (117) evaluated Complex Decongestive Physiotherapy (CDP) in 17 patients with unilateral severe leg lymphedema and found a significant reduction in circumference and in skin tissue water. Birkeballe et al (118) compared nine untreated patients with leg lymphedema with ten patients treated with compression bandaging. They found that the treated patients had a lower TDC ratio compared to the untreated patients, indicating that it is possible to evaluate compression treatment with TDC. More knowledge about the TDC method for evaluating treatment in mild BCRL was needed. At the time of planning the studies included in the thesis, TDC had not been used earlier to evaluate treatment with compression garment in mild BCRL. Also, there were only a few studies that had evaluated treatment with compression garment with WDM.

Measuring Health-Related Quality of Life

Traditionally, symptom relief, morbidity and mortality have been used as outcome measures in research. However, as medical, and public health advances have led to cures and better treatments of existing diseases and delayed mortality, perceived HRQOL has become an increasingly important issue. HRQOL assessments have evolved in the recent decades and has today an important role in the interpretations and conclusions of the research results (69). Minor treatment effects or benefits may be more than outweighed by the poorer HRQOL and cost of therapy (69). Moreover, HRQOL research is important in communication with patients, for example to obtain more information about the scope of the problem that may affect them, thus enable them to anticipate and understand the consequences of their illness and treatment (69).

Instruments measuring HRQOL can be either generic or disease specific. Generic instruments can be used to compare HRQOL in groups of different kind of diseases. Disease specific instruments are more sensitive to changes and can be used to detect differences in HRQOL between specific treatment groups or when following patients over time in longitudinal studies. There are rather few disease-specific instruments examining HRQOL in patients with lymphedema. Most studies of HRQOL in women with BCRL have used generic or cancer specific instruments and do not capture the specific symptoms experienced by BCRL patients (68). Lymphedema Quality of Life Inventory (LyQLI) is a disease specific instrument that includes most dimensions of HRQOL, including arm specific symptoms and can be used to compare different types of lymphedema (119, 120). At the time of planning the studies, the LyQLI was the only disease specific instrument available in Swedish.

Rationale

In the recent years it has been shown that early diagnosis and treatment of BCRL is important to prevent progression and development to a chronic disease. However, there is no consensus on how to detect and diagnose early mild BCRL, because new more sensitive methods for diagnosing and evaluating treatment are not sufficiently evaluated. There was a need to improve diagnostic methods and methods for evaluating treatment in early mild BCRL, which could benefit patients. Also, there was limited knowledge about the treatment effect of wearing compression garment and randomized studies examining the proportion of women with mild BCRL with no progression without treatment were lacking. Also, in a holistic perspective, the goal of the treatment is to improve HRQOL. In mild BCRL, wearing a compression garment can be experienced as negative and may have a negative impact on HRQOL. A small treatment effect or benefits with using compression garment may be outweighed by a poorer HRQOL and the cost of compression. To be able to individualize and optimize the effect of lymphedema treatment, more research was needed that evaluated if the use of compression garment had an impact on HRQOL. With this background an overall aim and specific aims were formulated.

Aims

Overall aim

The overall aim of this thesis was to evaluate diagnostic methods, treatment, and health-related quality of life in women with early mild Breast Cancer-Related Lymphedema (BCRL).

Specific aims

1. To evaluate the Tissue Dielectric Constant (TDC) and Water Displacement Method (WDM) in combination with palpation for early diagnosis of mild arm lymphedema, examine the association between TDC and WDM measurements and compare lymphedema related factors between groups diagnosed by these methods.
2. To examine if TDC and WDM can measure changes in mild arm lymphedema over a six month period of standard treatment. Also, to examine changes within and between three different groups based on lymphedema thresholds of TDC and WDM at start of treatment, as well as changes of the highest TDC value and site.
3. To investigate the proportion of women with mild arm lymphedema showing progression/no progression of lymphedema after treatment with or without a compression garment, and differences in changes of Lymphedema Relative Volume (LRV), local tissue water and subjective symptoms during six months. Adherence to the self-care regime was also examined.
4. To investigate if there is a difference in disease specific Health-Related Quality of Life (HRQOL), between women with mild BCRL wearing compression garment or not for 6 months.

Methods

Study designs

All four studies included in the thesis are based on a prospective clinical trial, where women with mild BCRL were randomized to the use of a compression garment or not and were called for follow-up visits after 1,2,3 and 6 months. The CONSORT checklist for Randomized Controlled Trials (RCTs) was followed, and the study was retrospectively registered in ISRCTN51918431. The study designs, participants, outcomes, and measurements are presented in Table 2.

Table 2. Overview of study designs, participants, outcomes, measurements.

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Design	Cross-sectional study at diagnosis.	Prospective longitudinal study for 6 months.	Prospective randomized controlled trial for 6 months.	Cross-sectional design,with assessments after treatment with compression garment or not for 6 months.
Partici-pants	72 women diagnosed with mild BCRL.	46 women with mild BCRL treated with compression garment.	70 women with mild BCRL treated with compression garment or not.	51 women with mild BCRL treated with compression garment or not.
Out-comes	Proportion with mild BCRL detected with WDM and/or TDC. Association between WDM and TDC measurements. Difference in lymphedema related factors between groups based on thresholds of TDC and WDM at diagnosis.	Changes in LRV and local tissue water at 1,2,3 and 6 months compared to baseline. Difference in change between defined groups based on thresholds of WDM and TDC at diagnosis. Changes of the highest TDC ratio and measuring site.	Primary outcome: Difference between groups in proportion having progression/no progression of LRV at 1,2,3 and 6 months compared to baseline. Secondary outcome: Difference in change between groups in LRV, local tissue water, and subjective symptoms at 1,2,3 and 6 months compared to baseline. Difference between groups in rated self-care at 6 months.	Difference between groups in HRQOL after 6 months treatment with compression garment or not.
Measure-ments Data sources	Arm volume was measured with WDM and local tissue water with TDC. Background data and frequency of self-care were retrieved from medical journals and one study-specific questionnaire.	Arm volume was measured with WDM and local tissue water with TDC. Background data was retrieved from medical journals and one study-specific questionnaire.	Arm volume was measured with WDM and local tissue water with TDC and subjective symptoms with VAS. Background data and frequency of self-care were retrieved from medical journals and two study-specific questionnaires.	HRQOLwas measured with LyQLI. Background data and self-care were retrieved from medical journals and two study-specific questionnaires.

Participants and their context

All participants in the studies (paper I-IV) were women treated for unilateral breast cancer after surgery with ALND (defined as removal of ≥5 lymph nodes in the axilla). They were diagnosed with mild BCRL at the Lymphedema Unit, Skåne University Hospital and at the Physiotherapy Cancer Unit, Karolinska University Hospital. Exclusion criteria were recurrent cancer (until 6 months before data collection), concurrent diseases, cognitive disability or unable to understand or speak Swedish.

Clinical criteria for definition of mild BCRL

Based on the research that was available prior to undertaking the clinical study, the criteria used to diagnose mild arm BCRL were:

- Increased skin and subcutis thickness (47) compared to the non-affected arm (30, 58) **and**
- Increased local tissue water, threshold TDC ratio (≥1.45 in the upper arm, **and/or** ≥1.3 in the forearm) (57), **and/or**
- Increased arm volume difference, threshold LRV ≥5 to ≤ 8% (42, 43).

Recruitment and randomization

Figure 6 shows the recruitment and number of participants in all four studies (paper I-IV). A total of 447 women treated for unilateral breast cancer and ALND were called for routine clinical follow-ups 4 to 6 weeks after surgery and 3 to 4 months after completed radiotherapy. They were also informed to return if lymphedema was noticed at any time. Of these, 96 women with mild BCRL were diagnosed, 75 women agreed to participate and were included in the project. The participants were consequently randomized to a compression group (CG) or non-compression group (NCG), by two of the authors, (KJ and KB), by picking a sealed envelope, in which the group allocation was stated. The randomization was done in blocks of 10 (allocation ratio of 1:1). The participants were called for visits after 1, 2, 3 and 6 months from diagnosis/baseline. The randomization, examinations, and treatment were carried out by two of the authors (KJ, KB) and by two other experienced lymphedema therapists (CS, PN), unblinded to the group allocation and to measurements at previous time-points.

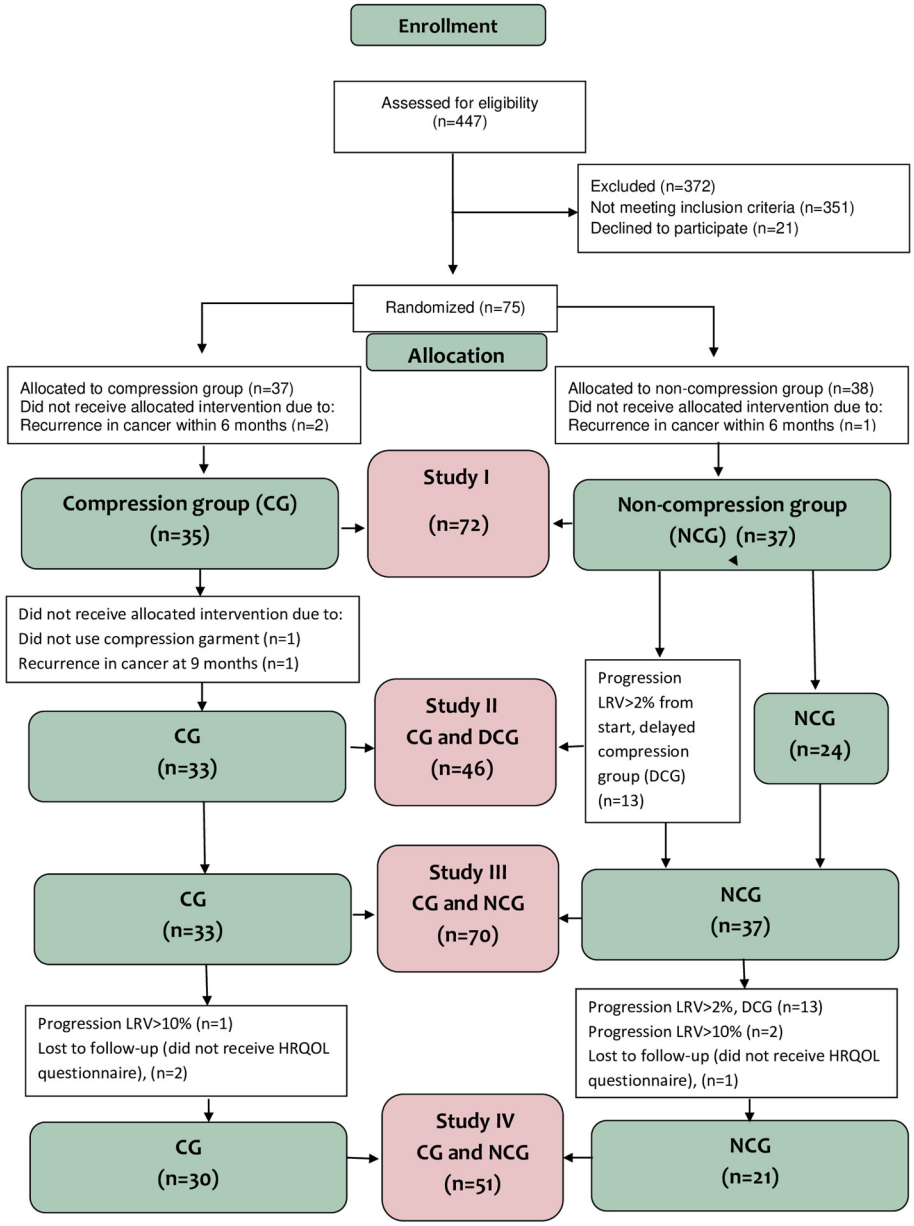

Figure 6. Flowchart showing recruitment and number of participants in study I-IV, included in the thesis.

Interventions

The CG received circular knitted compression sleeves (ccl 1) or if needed, individually adjusted compression sleeves (ccl 2) for daily wearing during six months, and education/counselling in self-care about exercise, weight control, skin care and instructions in self-massage. The self-massage comprised instructions on light strokes of shoulder and arm in proximal direction about 10-15 minutes a day. If the self-massage was perceived as effective, participants were encouraged to continue, if not they stopped. The NCG received instructions in self-care only. Due to ethical reasons, the participants in the NCG who increased LRV ≥2% from diagnosis/baseline dropped out from their group allocation and started to wear compression garments. If LRV exceeded ≥10% the participants from both groups dropped out and received extended treatment.

Data collection and outcome measurements

At diagnosis/baseline, data about surgical methods and adjuvant treatments were retrieved from medical records, and the participants responded to a study-specific questionnaire regarding age, education, and marital status. Measurements of arm volume, local tissue water, subjective symptoms, weight (kg), and garment pressure were performed at diagnosis/baseline and at 1,2,3 and 6 months. Also, height (in meter), was measured at diagnosis/baseline. At 6 months, questionnaires about physical activity/exercise/housework, HRQOL and adherence to recommended self-care were performed. Data were collected from September 2014 to April 2019.

Clinical examinations

Increased skin and subcutis thickness (paper I)

Palpation of increased skin and subcutaneous thickness was an inclusion criterion for diagnosis and performed simultaneously in both arms at the medial, ventral, and lateral sites (Figure 7). An increased thickness in the affected arm compared to the non-affected arm was noted (45). Skin thickness has been shown to correlate with the degree of swelling (46) and dermal backflow (47). Palpation combined with measurements of arm volume had previously been used to diagnose mild BCRL (30, 58).

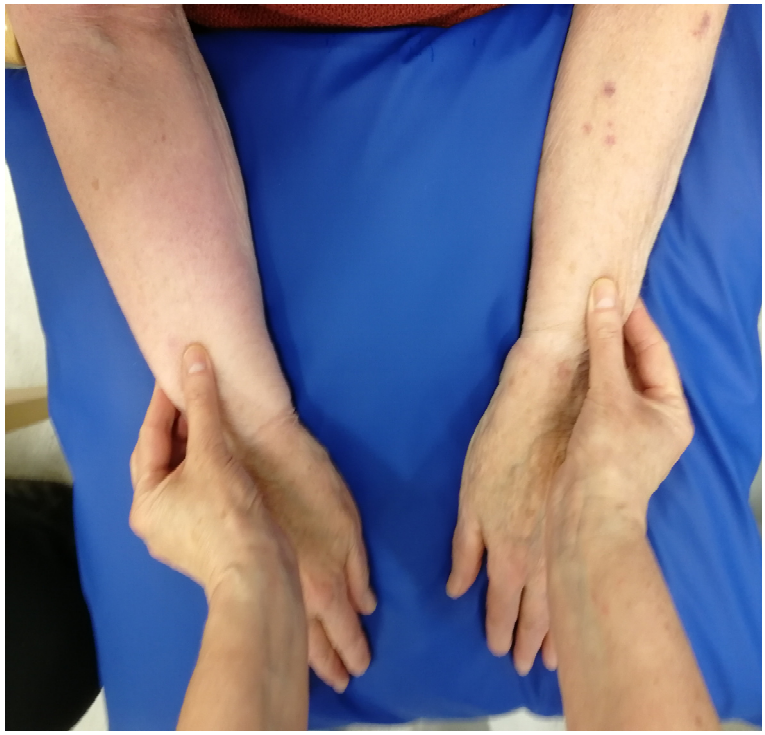

Figure 7. Palpation of increased subcutaneous thickness in skin and subcutis.© Karin Johansson

Local tissue water (paper I, II, III)

Local tissue water was measured with the MoistureMeterD or MoistureMeterD Compact (Figure 8), (Delfin Technologies Ltd, Finland) and used as an outcome parameter in paper I-III. The devices transmit a high-frequency electromagnetic (EM) wave at 300 Hz via the coaxial probe in contact with the skin to varying depths depending on the probe used. In articles I-III the probe with an effective penetration depth of 2.5 mm was used. Based on information of the reflected electromagnetic wave, the devices calculate the tissue dielectric constant TDC from the complex permittivity of the composite tissue. The TDC values is directly proportional to the tissue water content. In both devices, the measurement values are given in the same TDC units. TDC values 1 and 78.5 correspond 0 and 100% of tissue water contents, respectively (121).

Figure 8. Measurement with MoistureMeterD Compact. © Katarina Blom

Since the effective penetration depth of the EM field was 2.5 mm, the devices measure local tissue water in skin and upper subcutis. Each site was measured once according to Mayrovitz et al (61) at six anatomical sites: medially, frontally, and laterally 5 cm proximal and 5 cm distal to the antecubital fossa in both the affected and healthy arm (Figure 9) and the TDC ratio between the TDC values of the arms was calculated. If lymphedema was palpated more proximally or distally in the arm, complementary measurements were taken 15 cm proximal or distal to the antecubital fossa. A significant positive correlation has been found between arm TDC ratios and arm volume in women with BCRL ($p<0.001$, $r=0.690$) (62). For repeatability, Mayrovitz et al (122) measured upper arm and forearm in healthy women and found a standard error of measurement (SEM) of 0.03 and minimal detectable change (MDC) of 0.08. Sensitivity and specificity of the TDC method for early assessment of BCRL in anterior forearm and upper arm have been found to be 65.8% and 83.9%, respectively (58).

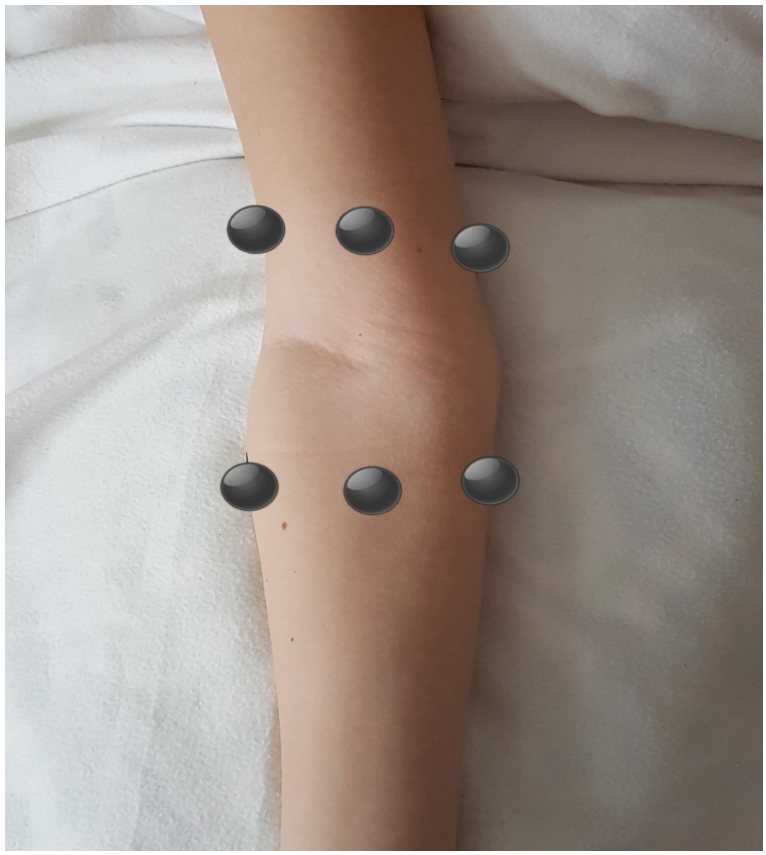

Figure 9. Measuring sites, at six points (medially, frontally and laterally).© Katarina Blom

Arm volume (paper I- IV)

Arm volume was measured using Water Displacement Method (WDM) and used as outcome measurement in paper I-III and as descriptive background data in paper IV. The measurements were performed with the elbow extended and the fists resting with the proximal phalanges on the bottom of a container filled with water; the contralateral arm was used as a control (Figure 10). Water displacement was measured in grams and converted into millimetres. LRV in percent, were obtained by calculating the difference in volume between the affected arm and the contralateral arm and adjusted by −1.5% if operated in the dominant arm and +1.5% if operated in the non-dominant (123). LRV has been used to quantify BCRL in the studies included in the thesis, because it is not correlated with a temporal change in weight (124). WDM has shown good reliability with an intraclass coefficient (ICC) of 0.99, measured in the same way as in our study, in patients with lymphedema in the upper extremity (125).

Progression of LRV (paper III, IV) was defined as an increase of LRV ≥2% compared to baseline or if exceeded LRV ≥10%, based on calculated SEM of 0.1 and a minimal detectable change (MDC) of 1.0% (116). There are only a few studies examining the validity of WDM, because the WDM method is considered the "gold standard" of volume measurements. However, Sagen et al (126) have conducted a validity test of the simplified water displacement instrument compared with computer tomography and showed a high correlation r=0.904.

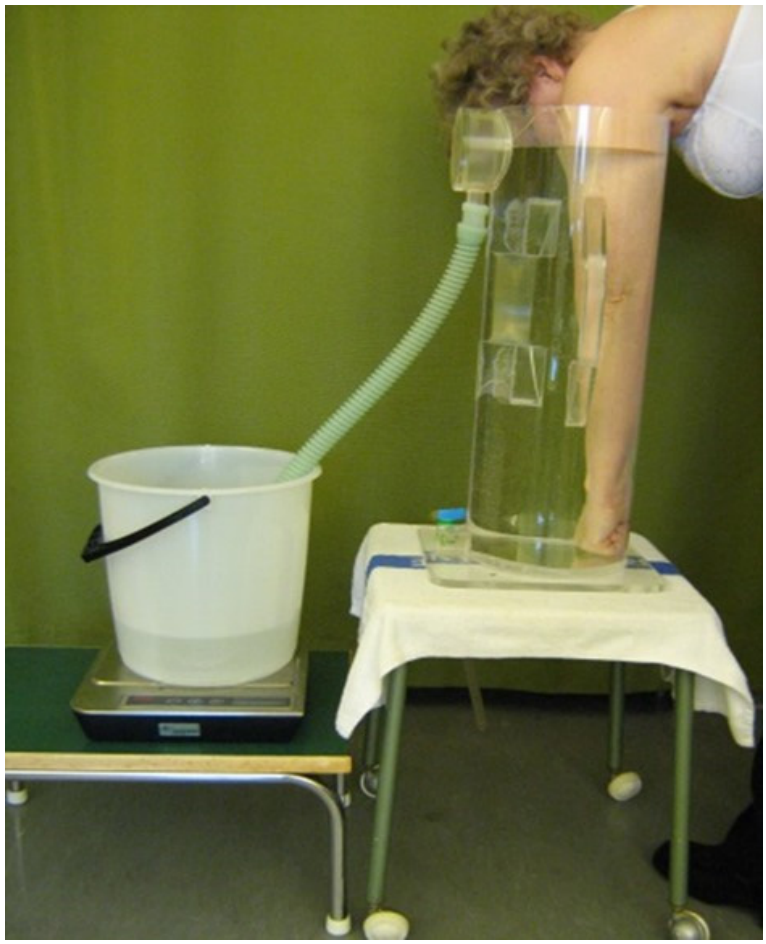

Figure 10. Measurement with Water Displacement Method (WDM). © Karin Johansson

Body mass index (BMI) (paper I- IV)

Body weight and height were measured to calculate BMI and used as descriptive background data in paper I-IV.

Pressure under the compression sleeve (paper II, III)

The pressure under the arm sleeve in the upper arm was measured using an air-filled pressure transducer (Kikuhine, TT Meditade, Sörö, Denmark) in the compression group and was used as descriptive background data in paper II and III.

Subjective symptoms (paper I, III, IV)

The participants self-rated experiences of heaviness, tightness, and pain in the affected arm were rated on a horizontal 100 mm Visual Analogue Scale (VAS) (127). The ratings were used as outcome measurements in paper III and as descriptive background data in paper I and IV.

Hand edema (paper I,III,IV)

The women were asked to self-rate the presence and degree of hand edema using a scale ranging from 0 (none) to 3 (very noticeable) (128). The ratings were used as descriptive background data in paper I, III, IV.

Questionnaires

Self-care (paper III, IV)

Self-care data were collected with a questionnaire concerning physical activity level/exercise and housework during the last four weeks on a six-point scale (from sedentary to high physical activity) (129). Frequency of self-massage was rated on a four-point scale (no massage, seldom, two-three times a week, every day), and use of compression garment on a three-point scale (not at all, half the day or the whole day). The self-care data was used as outcome measurement in paper III and as descriptive background data in paper IV.

Health-Related Quality of Life (HRQOL) (paper IV)

Disease specific HRQOL was measured with the Lymphedema Quality of Life Inventory (LyQLI) and was used as outcome measurement in paper IV. The instrument is translated into Swedish and contains 45 items and they are divided into three domains: physical (12 items), psychosocial (16 items) and practical (13 items). Each of these items assesses the impact of lymphedema on HRQOL on a 4-point Likert scale ranging from 0 = “None” or “not relevant” to 3 = “A lot”. A higher score indicates more negative impact on HRQOL. The questionnaire also includes four global items. Item 42 is a question on whether there had been a typical four-week period regarding the lymphedema and item 43 is a follow-up question if the period was not typical, on how the four-week period had been. Also, item 44 assesses the overall experience of lymphedema and item 45 the overall quality of life, both on a 4-point Likert scale ranging from “Very bad” to “Very good”.

A higher score indicates a higher overall HRQOL. LyQLI has shown a good reliability and validity (130). Reliability estimates using ICC for the physical domain were 0.88, for the psychosocial domain 0.87 and for the practical domain 0.87 (130).

Statistical analysis

A power calculation with a power of 0.85 at $p \leq 0.05$ level of significance at the time of planning study III, showed that 80 participants should be included to be able to detect an arm volume difference of 20% between the groups (30). However, we ceased recruitment when 75 participants had been included due to an unreasonably time-consuming recruitment and inclusion process. The HRQOL and TDC data were not normally distributed and therefore presented as both median (min-max) and mean±SD, to be able to compare results with other studies. An overview of statistical analysis in paper I-IV is presented in table 3.

Table 3. Overview of statistical analyses used in paper I-IV.

	Paper I	Paper II	Paper III	Paper IV
Descriptive statistics				
Number (n)	X	X	X	X
Proportion (%)	X	X	X	X
Mean (SD)	X	X	X	X
Median (min-max)		X	X	X
Quantitative				
Median difference (min-max)		X	X	
Mean difference (CI)		X	X	
Wilcoxon signed rank test		X		
Pearson Chi Square test	X		X	X
Fisher's exact test	X		X	X
Mann Whitney U-test			X	X
Independent T-test			X	X
Dependent T-test		X		
Kruska Wallis test	X	X		
One-Way Anova	X			
Spearman's correlation	X			
Dunn-Bonferroni correction		X		

In paper III, the participants who progressed in LRV≥2% from baseline or exceeded 10% was defined as having progression and remaining no progression. They dropped out and were not included in the LRV analysis, local tissue water, subjective symptoms, and self-care after the timepoint when progressed, but a post hoc analysis of LRV and local tissue water, were made and presented in paper III. In paper IV, the responses to the specific items of LyQLI were dichotomized into none/a little impact (score 0-1) and somewhat/a lot impact (score 2-3).

The differences in HRQOL between CG and NCG were calculated based on the original four response options in LyQLI (i.e., 0-3), using the Mann Whitney U-test. Missing items were substituted with the mean of the participant's responses (130). The analyses were carried out in IBM SPSS Statistics 24 (study I), 26 (study II, III) and 28 (study IV). A significance level of $p<0.05$ (two tailed) was chosen.

Ethics

All studies were performed in accordance with the ethical standards of the Helsinki Declaration (131). The Regional Ethical Board, Lund University approved the studies, D nr:2014/399. All participants received oral and written information where it was clearly stated that participation was voluntary and their withdrawal at any time, would not affect future contact or treatment with the healthcare. All participants gave their written informed consent to participate in the project. They were called for follow-up visits more frequently than usual care but did not have to pay for the follow-up visits. Data were coded to maintain anonymity and stored in a locked cabinet at the clinics to protect participants from being exposed.

Results

Methods to detect mild BCRL

In paper I, data from 72 participants diagnosed with mild BCRL were analysed (Figure 6). Their characteristics and baseline data are presented in paper I (Table 1). They were diagnosed early, with a lymphedema mean duration of 1 month and a mean LRV of 4.5%.

All women included had a palpable increased skin and subcutaneous thickness and were measured with both WDM and TDC. The proportion mild BCRL detected by TDC, WDM or both are shown in Figure 11. Totally, 74% were detected by the TDC and 55% by the WDM.

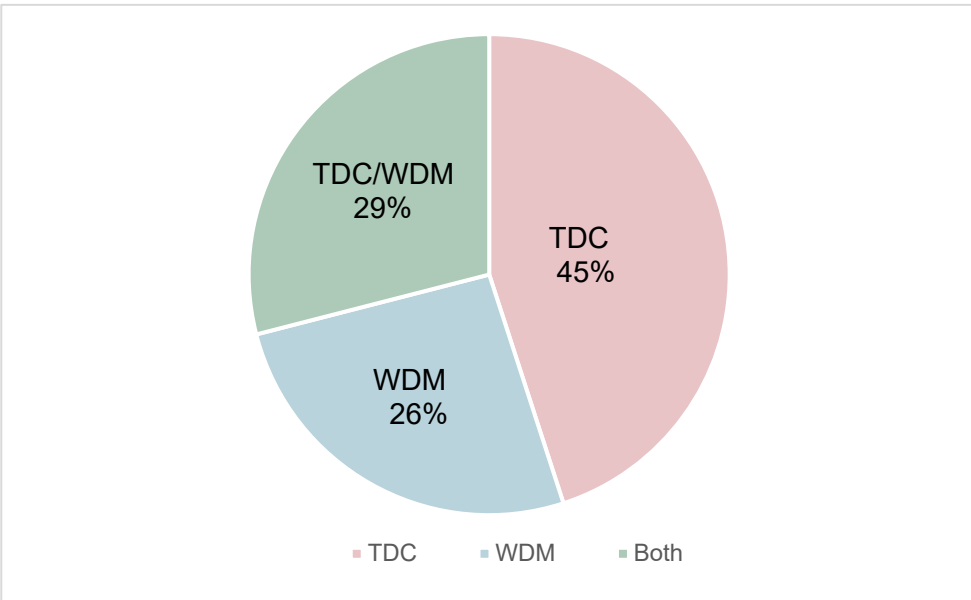

Figure 11. Proportion mild BCRL, detected with Tissue Dielectric Constant (TDC), Water Displacement method (WDM) and both TDC and WDM.

Association between local tissue water and lymphedema relative volume

There was a significant negative association between local tissue water (the highest TDC ratio in each woman), among all the six measured points (Figure 9) and LRV (rho = −0.545, p <0.001) respectively. For more details see Figure 1 in paper I.

Difference in lymphedema-related factors

A significant lower LRV was found in the TDC group (detected with TDC), on average 1.3 %, compared to the WDM group (detected with WDM) 6.3 % and the TDC/WDM group (detected with both TDC/WDM) 6.2 %, (p<0.001). The TDC group were diagnosed earlier after surgery (mean 4.1 months), compared to the WDM group (mean 9.1 months) and the TDC/WDM group (mean 6.7 months), (p=0.003).

TDC diagnosis site

Among the participants in the TDC group and TDC/WDM group, 85% of the highest TDC ratio exceeding thresholds were found at the medial site close to the antecubital fossa in the upper arm and forearm or both medial sites. For more details see Table 2 in paper I.

Methods for evaluating standard treatment

In paper II, data from 46 participants were analysed (Figure 6). They got standard treatment including self-care and treatment with compression garment and were followed for 6 months. Patient characteristics and baseline data are presented in paper II (Table 1).

Changes in local tissue water

The highest TDC ratios at start of treatment among all the participants were found in the upper arm medial (median 1.26), and in the forearm medial (median 1.16), (Paper II, Table 2). At one month, there was a significant decrease in the forearm medial (median difference -0.05, p=0.021), and close to significant in the upper arm medial, (median -0.03, p=0.059), compared to start (Paper II, Table II). The other sites had lower median TDC ratios at start of treatment (range: 1.03-1.09) and maintained low median TDC ratios (range: 1.04-1.09) for 6 months. However, there was a significant increase of TDC ratio in the upper arm lateral (median + 0.03, p=0.048) at one month, and a significant decrease in the forearm ventral (median -0.06, p=0.037) at sixth month.

There was a significant decrease in the site with the highest TDC ratio, at all follow-up visits, both when the same site and the highest TDC ratio by any site was followed, ($p<0.05$). The largest decrease was found at one month with a median difference of -0.19, compared to start, when the same site was followed (Table 4).

Table 4. Changes in the highest TDC ratio over 6 months standard treatment, n=46

	Highest TDC ratio Same site followed	**Highest TDC ratio By any site followed**
Start TDC ratio (min-max)	1.47 (1.08-1.96)	1.47 (1.08-1.96)
1 month Median difference (min-max) p-value	-0.19 (-0.84-0.29) <0.001*	-0.04 (-0.84-0.29) 0.028*
2 months Median difference (min-max) p-value	-0.24 (-0.81-0.28) <0.001*	-0.12 (-0.56-0.36) 0.002*
3 months Median difference (min-max) p-value	-0.28 (-0.94-0.52) <0.001*	-0.08 (-0.71-0.53) 0.002*
6 months Median difference (min-max) p-value	-0.24 (-1.04-0.37) <0.001*	-0.11 (-0.62-0.96) 0.006*
*Significant change from start,p<0.05, Wilcoxon signed rank test, related samples		

Changes in LRV

There was a significant decrease ($p\leq0.001$) in LRV at all follow up-visits with a mean difference of -3.3% at 6 months. The largest decrease in LRV was found at one month, with a mean difference of -1.9%, ($p=0.001$), (Table 5).

Table 5. Changes in lymphedema relative volume (LRV) over 6 months standard treatment, n=46.

Start LRV ±SD, % [a]	**4.9±3.4 %**
1 month Mean difference (CI), % p-value	-1.9 (-3.0,-0.9) 0.001*
2 months Mean difference (CI), % p-value	-2.8 (-3.9,-1.6) <0.001*
3 months Mean difference (CI), % p-value	-2.6 (-3.7,-1.6) <0.001*
6 months Mean difference (CI), % p- value	-3.3 (-4.5,-2.1) <0.001*
*Significant change from start, p<0.05, t-test, related samples. [a] LRV= Lymphedema relative volume, adjusted with -1.5% if surgery in the dominant arm and +1.5% of surgery in the non-dominant arm.	

Differences in changes between defined groups

There was a significant difference in change of local tissue water between the three defined groups (TDC group, TDC/WDM group and WDM group, based on thresholds at diagnosis), at first and third month, when the highest TDC ratio at the same site was followed. At three months, the TDC-group had the largest decrease with a median difference (-0.47), compared to the TDC/WDM-group (-0.25) and the WDM-group (-0.06), (p=0.003), (Paper II, Table 5).

There were no significant differences between the groups in change of LRV at any of the follow-up visits. At sixth months the TDC/WDM group had decreased with a median difference of (-4.2%) compared to TDC-group (-2.9%) and WDM-group (-2.8%), (Paper II, Table 5).

Change of highest TDC ratio and site

Among all six TDC measuring sites, 59.5% had changed the site of the highest TDC ratio to another site. Of all these, 52 % had changed site from forearm to upper arm, 16% had changed site from upper arm to forearm, 20 % had changed site in the forearm, and 12 % had changed site in the upper arm.

The effect of compression treatment vs no compression

In paper III, a total of 70 participants were analysed, 33 in the CG and 37 in the NCG (Figure 6). Patient characteristics and baseline data are presented in paper III (Table 1). The participants in the CG and the NCG were comparable in baseline data, except for surgery. In the CG, 61% had underwent surgery with mastectomy, compared to 35% in the NCG, (p= 0.033).

A significant smaller proportion in the CG had progression (exceeded LRV≥2% from baseline or exceeded 10%), compared to the NCG at 1,2 and 6 months. At 6 months, 16% showed progression in CG compared to 57% in the NCG, (p=0.001), and 84% in the CG, showed no progression in LRV compared to 43% in the NCG (Table 6).

Table 6. Proportion of participants with no progression/ progression in compression group (CG) and non-compression group (NCG).

Start	CG N=33	NCG N=37	p-value
1 month Lost to follow-up, n No progression, n (%) Progression, n (%)	 1 31(97) 1 (3)	 2 26 (74) 9 (26)	0.005*
2 months Lost to follow-up, n No progression, n (%) Progression, n (%)	 2 29 (94) 2 (6)	 0 25 (68) 12 (32)	0.013*
3 months Lost to follow-up, n No progression, n (%) Progression, n (%)	 1 27 (84) 5 (16)	 0 22 (60) 15 (40)	0.057
6 months Lost to follow-up, n No progression, n (%) Progression, n (%)	 1 27 (84) 5 (16)	 0 16 (43) 21 (57)	0.001*
'Significant difference between groups, p<0.05, Fisher's exact test			

Difference in change of mild BCRL between groups

The CG had a larger decrease in LRV at all time points. At 6 months, CG decreased (-3.8%) compared to NCG who remained stable (+0.1%), (p<0.001), (Table 7)

Table 7. The Lymphedema relative volume (LRV) over 6 months in the compression group (CG) and non-compression group (NCG).

	CG N=33	NCG N=37	p-value*
Baseline LRV[a] ±SD, %	 4.4±3.1	 3.8±3.5	 0.456
1 month Mean difference (CI), %	 -1.9 (-3.1,-0.7)	 0.3 (-0.7,1.3)	 0.005*
2 month Mean difference (CI), %	 -2.6 (-3.9,-1.4)	 -0.1 (-1.0,1.1)	 0.001*
3 month Mean difference (CI), %	 -2.6 (-3.7,-1.6)	 -0.1 (-1.1,1.0)	 0.001*
6 months Mean difference (CI), %	 -3.8 (-5.0,-2.5)	 0.1 (-1.2,1.3)	 <0.001
*Significant difference in change from baseline, p<0.05,Independent T-test Adjusted with +/- 1.5% if surgery in non-dominant/dominant side			

Also, the CG had a larger decrease in the highest TDC ratio at 6 months, when the same site was followed, with a median change of -0.28 in the CG compared to -0.10 in the NCG, (p=0.025), (Table 8).

Table 8. Local tissue water measured with Tissue Dielectric Constant (TDC) over 6 months in the compression group (CG) and non-compression group (NCG.

TDC ratio highest value Same site followed	CG n=33	NCG n=37	p-value*
Baseline TDC ratio (min-max)	1.50 (1.09-1.96)	1.55 (1.05-2.15)	0.805
1 month Median diference (min-max)f	-0.23 (-0.84-0.29)	-0.20 (-0.94-0.43)	0.609
2 month Median difference (min-max)	-0.29 (-0.81-0.28)	-0.16 (-0.94-0.94)	0.059
3 month Median difference (min-max)f	-0.30 (-0.94-0.28)	-0.07 (-0.99-0.64)	0.053
6 months Median difference (min-max)	-0.28 (-1.04-0.30)	-0.1 (-1.0-0.4)	0.025*
*Significant difference in change from baseline, p<0.05, Mann-Whitney-U test			

Subjective symptoms

There were no differences between the CG and NCG in self-rated subjective symptoms of tension, heaviness, and pain, at any time point. However, there was a significant difference in change of tension, at 1 month, where the CG decreased more than the NCG, median difference (min-max): 0 (-56 to 29) vs 0 (-45 to 39), (p=0.008).

Adherence to recommended self-care

At 6 month, all 33 women in the CG rated that they wore the compression garment. Of these, 93% the whole day, and 7% half the day. There were no differences between CG and NCG in self-rated frequency of physical activity/exercise and housework, or frequency of performed self-massage.

Impact on HRQOL of wearing a compression garment

In paper IV, 51 participants were analysed, 30 in the CG and 21 in the NCG (Figure 6). Patient characteristics and baseline data are presented in paper IV (Table 1). The women in CG and NCG were comparable in background data, except for LRV at 6 months due to randomization to compression garment or not.

Both CG and NCG experienced a low impact on HRQOL in all domains, but the CG experienced a significantly higher impact on HRQOL in the total score of the practical domain compared to the NCG (Figure 12), (p=0.026).

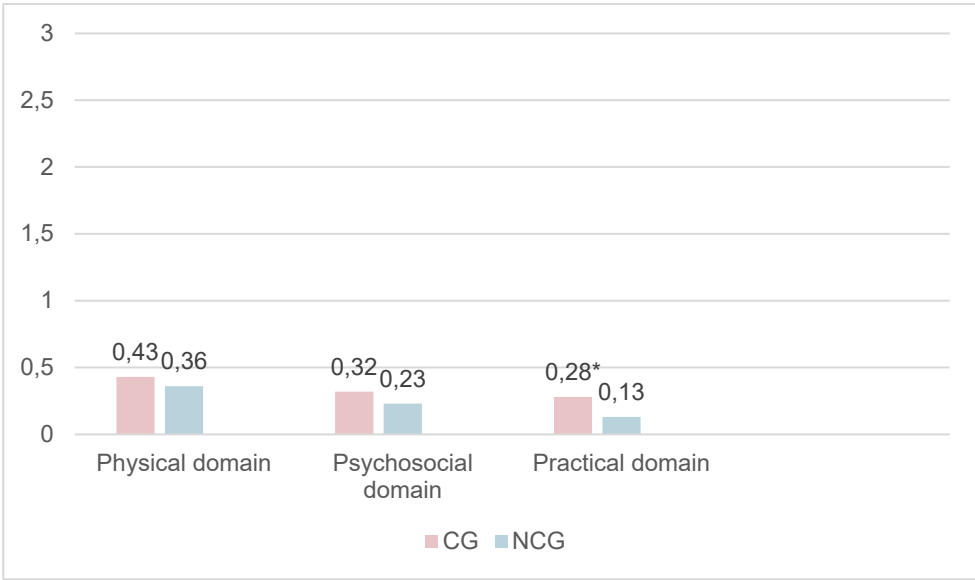

Figure 12. Mean scores for compression group (CG) and non-compression group (NCG) in the physical, psychosocial and practical domain, measured with LyQLI. Score options 0-3. A score below 1 indicates a minor negative impact on HRQOL. * Significant difference, $p<0.05$, Mann Whitney-U test

In the practical domain, the CG experienced a higher impact in the items *employment activities* (p=0.019), *finding well-functioning compression garments* (p=0.031) and *limitations in hot weather/sun* (p=0.046), (Paper IV, Table 3). In the psychosocial domain, the CG experienced a higher impact in the items *feelings of embarrassment by lymphedema/compression garments* (p=0.015), *feeling discomfort/embarrassment while doing sports and hobbies* (p=0.036) *and having to answer questions about the lymphedema* (p=0.011).

Most women in both CG and NCG experienced an overall high HRQOL. In the CG, 100% experienced good/very good overall experience of lymphedema related to HRQOL, compared to 90% in the NCG. Also, 97% in the CG experienced good/very good overall quality of life, compared to 90% in the NCG, (Paper IV, Table 3). There were no significant differences between the groups in overall experience of lymphedema related to HRQOL (item 44); mean±SD in CG/NCG, 2.59±0.50/2.55±0.69 or in overall quality of life (item 45), mean±SD in CG/NCG, 2.38±0.56/2.55±0.69.

Discussion

General discussion

The overall aim of this thesis was to evaluate diagnostic methods, treatment, and HRQOL in women with early mild BCRL. In the model of cancer rehabilitation, the research was conducted on the basic level of care, containing diagnosis and initial treatment phase, where the goal is secondary prevention. In study I-III we examined physical impairments as LRV, local tissue water and subjective symptoms related BCRL. In study IV we examined disease specific HRQOL with LyQLI. LyQLI, includes several aspects according to ICF and assesses physical impairments, activity limitations, and participating restrictions but also personal and environmental factors related to BCRL.

More women with mild BCRL were detected using the TDC method in combination with WDM, compared to only using the WDM method. Both TDC and WDM could detect changes during standard treatment, but the methods measure different aspects of lymphedema and need therefore to be interpreted separately. Furthermore, immediate treatment with compression garment could prevent progression of mild BCRL, compared to no compression treatment. The participants with mild BCRL experienced a high overall HRQOL, but those wearing compression garment experienced a higher negative impact on HRQOL in the practical domain and in some of the psychosocial items, compared to those not wearing compression garment. This thesis has added new knowledge that can improve diagnosis, and treatment in women with early mild BCRL, thus preventing progression of mild BCRL and negative impact on HRQOL. The increased knowledge has importance for clinical decision making, patient education and planning of future clinical studies.

Methods to detect mild BCRL

In paper I, the TDC and WDM methods were evaluated for detection of early mild BCRL and the results showed that both TDC and WDM, together with skin palpation can be used to diagnose early mild BCRL.

Of all participants diagnosed with mild BCRL,74% were detected by TDC, compared to 55% by the WDM, showing that the TDC method was the most valid method to detect early mild BCRL. However, the WDM method was also needed. This shows the importance to both use more sensitive methods than WDM and a combination of methods to be able to detect mild BCRL. Thomis et al (47) investigated concurrent validity between clinical assessments and near infrared lymphoflouroscopy and they also found that the clinical assessments of skinfold thickness, water content and lymphedema volume are the most appropriate tools to detect dermal backflow. In paper I, results showed that 26% of the mild BCRL was detected by WDM. One explanation may be that the TDC measure only the most superficial parts of the dermal backflow in the epifaschial tissue, and if we had a probe with a deeper measuring depth, we would perhaps also have diagnosed these patients. Other explanations may be that the thresholds used in paper I was too high, or that it is an individual variation in how lymphoedema starts and develops. Suami et al (132) found areas of dermal backflow in mild lymphedema when the collecting vessels were still functioning, but with time when the lymphedema become more severe, and the collecting vessels are damaged, no dermal backflow could be detected. Also, Dylke et al (133) found that 14% who were diagnosed with lymphedema but had no dermal backflow. However, the women in that study had been diagnosed with a lymphedema at 40 months of its presence opposed to the 1-month duration in paper I.

Moreover, in paper I, the participants with mild BCRL, detected by TDC, were detected earlier after surgery and they had a lower LRV (1.3%) than those detected by WDM only (6.3%) or both TDC/WDM (6.2%). Also, a negative association (rho = −0.545), between the highest TDC ratio of each woman and LRV was found, indicating that the first signs of lymphedema began in the subcutis. The increased local tissue water in skin and upper subcutis, indicate presence of dermal backflow. With time, by creating alternative pathways through dermal backflow, or maybe due to a larger amount of fluid and damaged lymph vessels, the lymphedema fluid may have moved into deeper tissue, explaining the lower TDC ratio but higher LRV over time, in accordance with the findings of Suami et al (16, 132).

Evaluation and effect of compression treatment

In paper II, changes in mild BCRL by TDC and WDM over six months standard treatment, including self-care and use of compression garment were examined. The results showed that both TDC and WDM could detect a significant reduction in arm lymphedema. The highest TDC ratio decreased significantly at all follow-up visits, compared to start, both when the same site was followed and by any site. At one month, the decrease was on average -0.18, and at six months -0.26, when the same site was followed.

Mayrovitz et al (122) measured TDC ratio in the forearm in healthy women and found a mean SEM of 0.029 and an MDC of 0.08. Also, De Vrieze et al (134) measured local tissue water in women with BCRL at 5 locations in the arm and found a mean SEM between 0.07-0.17, depending on which measuring site. Moreover, in paper II, there was a significant decrease in LRV at all follow-up visits, compared to start. At one month, the decrease was on average -1.9 % and at six months -3.3%. Karges et al (125) performed the measurements in a similar way as in the present study, with the finger fixed at the bottom of the container and found a SEM of 0.1% and Hidding et al (116) calculated a MDC of 1.0 %. Thus, the results in paper II indicated that the decrease in local tissue water (TDC ratio) and LRV was larger than the normal measurement variability and that both the TDC and WDM method could detect changes during standard treatment.

In paper I, 85% of the mild BCRL, detected by TDC was found in the medial upper arm, the medial forearm, or at both sites. These results are consistent with clinical experience in which one often can palpate a thickness at the medial site and in accordance with findings of Lahtinen et al (58). They also diagnosed a high percentage (66%) at the medial site in upper arm and forearm, though being the only sites measured. Furthermore, we also found that in almost all cases a positive lateral and ventral/frontal TDC ratio in the upper arm or forearm was associated with a positive medial TDC ratio, indicating that it is not necessary to measure these sites. Measuring on the frontal side also carries a risk for error from having venous vessels too close to the measuring points. In paper II, at first month, there was a significant decrease in local tissue water at the measuring sites in the forearm medial and a close to significant decrease in the upper arm medial. The results confirmed that the medial sites are appropriate to measure, not only to detect early mild BCRL (paper I), but also to evaluate treatment (paper II).

In paper III, the effect of treatment with compression garment or not for 6 months was examined, and the results showed that immediate treatment with compression garment could prevent progression in mild BCRL. There were significantly fewer participants who showed progression of LRV in the CG, compared to the NCG. At 6 months, in the CG, 16% had progression (LRV≥2% from diagnosis/baseline or exceeded 10%), compared to 57% in the NCG. At 6 months, the CG decreased in LRV, on average -3.8 %, compared to +0.1 in NCG who remained stable (due to exclusion of participants who progressed in LRV). The results in paper III, are in line with the study by Stout-Gergich et al (41) who evaluated treatment with a compression arm sleeve, for 4 weeks and found a mean LRV decrease of -2.4%, on average 4.6 months from start of intervention. Also, there was a significant difference in change of the highest TDC ratio between the groups at 6 months when the same site was followed. The CG decreased median -0.28, compared to -0.10 in the NCG. However, there may have been significant results at the other time-points if the patients with progression had been included in the analysis.

These results in paper III, showed that immediate treatment with compression garment is important and effective to prevent progression in mild BCRL.

Furthermore, in paper III, 43% of the participants in the NCG had no progression of LRV, and these women could manage without treatment with compression garment. This is an important result that should be considered in all research of early mild BCRL, as well as in clinical settings. A previous study has found that preventive use of a compression garment after ALND can decrease the incidence of arm lymphedema with 10% (135). However, of all breast cancer patients treated with ALND, with a calculated lymphedema incidence of 40% (30), preventive use of compression garment would benefit only 23% of the patients. Also, the use of compression garment has a minor negative impact on HRQOL (paper IV). The result in paper III and IV indicates that preventive use of compression garment for all patients treated with ALND can be questioned and will put an unnecessary burden on the patient and a higher cost for both the patient and the health care system. Therefore, we recommend regular follow-ups/screening for early BCRL after surgery and initiating treatment with compression garment at diagnosis.

Moreover, self-rated subjective symptoms in the arm were generally low at all time-points and did not differ between the groups (paper III). The results are consistent with previous research showing a correlation between perceived symptoms and the degree of lymphedema volume (136). Regular examinations of women at risk are therefore even more important, because women with mild BCRL do not necessarily have subjective symptoms in the arm and may not be attentive to onset of lymphedema. A significantly larger reduction of tension was found in the CG compared to the NCG at first month in paper III. Also, there was a significant decrease in both LRV and local tissue water at first month (paper II). This indicates that use of compression garment may have a fast positive effect on perceived tension in the arm. The possible explanation may be that the compression garment decrease the LRV and pressure on the tissue, but it also has an anti-inflammatory effect (91), and may therefore reduce subjective symptoms.

In paper II, the results showed a significant difference between the defined groups (based on thresholds of TDC and WDM at diagnosis) in change of local tissue water, where the TDC group and TDC/WDM group had the largest decrease in TDC ratio during the intervention, but the decrease in LRV was similar in all groups. Therefore, the WDM method was more useful when evaluating treatment, compared to the TDC. Also, the difference in decrease between the defined groups showed that it is important to interpret the TDC and WDM values separately depending on which values are above thresholds at start of treatment. Surprisingly, participants in the TDC group also had a similar decrease in LRV as the other defined groups, even though they had a very low LRV, on average 1.4%, at start of treatment. This shows that the participants in the TDC group also had benefit of treatment and indicate that these participants already had an increase in LRV at diagnosis.

Therefore, in the clinic, when there is no access to preoperative LRV values, the WDM method alone is not sensitive enough to detect an early mild BCRL (paper I).

From previous studies, we know that compression treatment reduces LRV (87). However, the effect on local tissue water was unknown. In paper II, the results showed a significant decrease in the highest TDC ratio, followed at the same site, and a significant but smaller reduction in TDC ratio when the highest TDC ratio at any site was followed, indicating that the compression garment has effect on local tissue water. However, in paper III a significant difference between the CG and NCG only at 6 months was found, showing that the local tissue water decreased more in the CG. The non-significant results at the other time-points may be explained by exclusion of the participants who progressed. Moreover, the measuring site with the highest TDC ratio changed to another measuring site from start to six months in about 60% of the women (paper II). Of these, 52% had changed the highest measuring site from forearm to upper arm, which probably is an effect of the compression treatment. Akita et al (17) examined patients with BCRL and they also found that the lymphatic function (measured by indocyanine green lymphography) improved by compression treatment, and these patients who had improvements had developed new collateral routes. A possible explanation of the improvement in local tissue water may be that the compression garment moves the superficial lymph fluid to other areas (88) where not affected lymph collectors are able to transport the lymph fluid back to the venous system. Also, the improved lymphatic circulation (88) may relieve the superficial lymphatic system, related to the correlation between subfascial drainage and epifascial arm edema (18). The results in paper II indicated that the total local tissue water had decreased during treatment but may in some cases have moved to other parts of the arm. Thus, it may be important to monitor several TDC measuring sites, when evaluating treatment.

Impact on HRQOL of wearing a compression garment

In paper IV, disease specific HRQOL in women with BCRL, 6 months after randomized to treatment with compression garment or not was investigated. The CG experienced a higher negative impact on HRQOL in the practical domain compared to the NCG, despite that the CG had decreased more in arm volume after 6 months treatment with compression garment. The results indicate that small changes in LRV do not have an impact on HRQOL. Rather, it seems that the use of the compression garment affects HRQOL more than the small increase in lymphedema volume. The difference between the CG and NCG in the practical domain was small and does not tell if the difference is of clinical importance. However, we do know from clinic experiences and some qualitative studies that some patients may perceive use of garment as negative (79, 80).

We also know that some patients with early symptoms of lymphedema, in particular a feeling of tension in the tissue, experience reduced tension after the application of a compression garment (paper III). Therefore, it is important to have a person-centered approach and identify the patient's own experience and consider the possible negative impact on HRQOL in relation to the preventive effect. If the patient chose to not wear compression garment, it is important to have a new follow-up visit within 3 months of diagnosis, when the risk of progression is greatest (paper III).

In the practical domain, the CG experienced a higher impact in items *employment activities, finding well-functioning compression garments and limitations in hot weather and sun* compared to the NCG. It is easy to understand these experiences. In many occupations, of hygienic reasons it is difficult to wear a compression garment, and in hot weather it can be both physically and mentally difficult. In view of this, compression treatment should be regularly evaluated to not place an unnecessary burden on the patient. Individualized counselling about strategies on how to use the compression garments in summer or during work/household activities may be helpful and may improve HRQOL. The difference between the groups in finding well-functioning compression garments can only be related to that the item was not at all relevant to the NCG.

In the psychosocial domain, the CG experienced a higher impact in the items *feelings of embarrassment by lymphedema/compression garments, feeling discomfort/embarrassment while doing sports and hobbies and having to answer questions about the lymphedema,* compared to the NCG. Similar psychosocial problems have been reported in a previous review (76). It can be helpful for the patients to discuss these feelings with the healthcare staff or other patients with lymphedema. Results in paper IV emphasizes the need of regular follow-up visits including education/counselling about self-care strategies and psychosocial support to improve HRQOL. In a paper III, 43% of the women diagnosed with mild BCRL, not treated with compression garment, did not progress in lymphedema volume and symptoms of tension, heaviness and pain were low. Therefore, the use of compression garment needs to be evaluated regularly and its potential impact on patient HRQOL should also be considered and discussed with the patients.

Methodological considerations

Design and generalizability

All four studies included in this thesis are based on the same material from the randomized controlled trial (paper III).

A power calculation, at the time of planning the study, showed that 80 participants should be included to detect a difference in LRV of 20% between the groups.

However, the recruitment was ceased when 75 participants had been included due to an unreasonably time-consuming recruitment and inclusion process and we had to exclude these participants who progressed, which may have affected the results. Strengths with the studies were the design with several follow-up visits during six months (paper II, III), few missing data in all studies (paper I-IV) and access to data of rated self-care. Also, almost all the measurements were performed by the same two experienced lymphedema therapists. However, a limitation was that the assessors were not blinded due to practical reasons. Moreover, lymphedema is expected to progress without treatment, and of ethical reasons, treatment was given to participants in the NCG who progressed in lymphedema relative volume. They received treatment with compression garment and were not included in the analyses of arm volume, local tissue water and subjective symptoms (paper III, IV) and this may have contributed to non-significant results. On the other hand, it was therefore possible to evaluate the isolated effect of treatment with compression garment and the consequences for HRQOL without any influence of these participants who progressed. Another limitation was the inclusion of participants that only could read and speak Swedish. It would have been optimal to be able to translate the questionnaires to other languages and include all patients. The studies are performed in a Swedish cohort, carried out under Swedish conditions and healthcare system. The results can be generalized to patients with early mild BCRL also in other countries, but only according to our definition of mild BCRL and early onset of treatment. Probably, there may be other results in patients with more severe BCRL and later onset of treatment.

Measurement methods

Traditionally, volume measurements with either WDM or circumference measurements with a tape measure have been used to diagnose and evaluate lymphedema treatment. In the clinic, circumferential arm measurements with tape are often used when diagnosing lymphedema and evaluating treatment. Tape measurements are practical and can easily be calculated to arm volume using the formula of the truncated cone (137). However, in the present studies, WDM was used, because WDM is by many considered as the “gold standard” of volume measurements and is often used as reference method when comparing with other methods. The WDM method is a valid (126, 138) and reliable method (116). However, the reliability of the WDM varies, depending on how the measurements are performed. Deltombe et al (139) examined reliability of WDM with the patients putting their arm into a cylinder up to a demographic skin mark located 15 cm below acromion and found an intra-rater lymphedema relative volume difference of 2.9%.

In the studies included in this thesis, we performed the measurements with the fists resting with the proximal phalanges on the bottom of the container, which may have improved the reliability of the measurements. Karges et al (125) measured in a similar way as in our study with fixed fist or fingers at the bottom of the container and Hidding et al (116) calculated a SEM of 0.1% and MDC of 1.0% based on that study.

There is no consensus on how to diagnose mild BCRL and our results depend on the definition of mild BCRL, and the thresholds used for WDM and TDC. However, a strength is the combination of methods for diagnosing mild BCRL. The inclusion criterion of palpation of increased skin and subcutaneous thickness, has shown to correlate with the degree of swelling (46) and dermal backflow (47). Also, LRV ≥5% is recommended for early diagnosis (42, 43) and the TDC thresholds (upper arm 1.45 and forearm 1.30) +3SD of mean (57) have probably reduced the risk of false positive lymphedema. There are other studies suggesting a TDC ratio threshold of 1.20 for diagnosis of BCRL (63, 140). However, these studies examined women with a lymphedema duration of several years and this may be too low threshold when detecting early mild BCRL without any increase in lymphedema volume.

At the time of planning the studies, there was limited information on the optimal assessment sites with TDC. Previous studies with TDC had chosen to measure on the ventral site of the arm (57, 140). We chose to measure at six fixed sites and where the lymphedema was palpated. The findings in paper I and II showed that the highest thresholds were located at the medial sites of the arm. These findings were consistent with our clinical experience of palpation of increased skin thickness. Also, Yang et al (60) diagnosed BCRL with Subcutaneous echogenicity grade (SEG) and they concluded that it was appropriate to measure at the medial region in the forearm.

A limitation in study IV, may be that a high proportion of the participants had a very small arm lymphedema and rated low scores in all domains showing low impact on HRQOL which may have resulted in a “floor effect” with non-significant results. However, there was some significant differences between the groups, indicating that the instrument was sensitive enough. Also, no minimal important difference of the instrument was reported and therefore we do not know if the significant differences between the CG and NCG are of clinical importance. Moreover, some of the items concerning the use of compression were not relevant for the participants in the NCG and they had to answer 0 for both "Not relevant” and "None". The differences in HRQOL in these items may arise from treatment differences, which may have affected the results. On the other hand, if the items regarding compression had been excluded, we would not have been able to find out how the use of compression garment affected HRQOL.

Ethical considerations

All participants received oral and written information where it was clearly stated that participation was voluntary and their withdrawal at any time, would not affect future contact or treatment. However, in randomized studies, it can be experienced that one does not have the opportunity to choose treatment, which infringes on women's autonomy. An ethical dilemma in the present studies may be that it was the same lymphedema therapists who offered participation in the study and performed the examinations and treatment. The women may have felt that they were in a position of dependence and did not feel free to say no to participation. For that reason, I have been particularly concerned not to force patients to participate and that those who refused the study would receive equally good treatment. However, the most optimal thing would have been if there had been one more lymphedema therapist who had been able to perform the examinations. Beauchamp et al (141) presents four principles to consider in ethical decision-making including autonomy, beneficence, nonmaleficence and justice. The principle of autonomy was considered in the studies and means that the person must be competent in decisions, have relevant information and not feel coercion or pressure, as well as the ability to absorb information and evaluate action alternatives.

The participants who were randomized to no compression were carefully followed and if they progressed more than 2% in lymphedema relative volume from diagnosis, they dropped out from the study and started compression treatment. Some women who were randomized to use compression garments had a very small lymphedema and no subjective symptoms. In these cases, the patients may have been treated unnecessarily. On the other hand, we did not know whether these women still benefitted from using compression garment and if a progression had been prevented. Also, the study aim, to examine if use of compression garment in mild BCRL, can prevent progression of the lymphedema is an important research question and the results were expected to have major clinical implications. The research results could be expected to benefit the study population in a whole, which may provide ethical validity to the studies (142). The principle of nonmaleficence and beneficence incorporates that harm have been minimized and benefits maximized (141), and these ethical principles were considered.

However, because we could not include participants who could not understand the Swedish language, the principle of justice that stands for the concept of an equal distribution of burdens and benefits among all possible participants, i.e., no exclusion based on socioeconomic class, gender, race, ethnicity, or age (141), could not be fully met.

Conclusions

In conclusion, this thesis has increased knowledge about diagnostic methods, treatment, and health-related quality of life in women with early mild BCRL.

Main conclusions

- TDC and WDM can be used together with palpation of skin and subcutaneous thickness for early diagnosis of BCRL, but TDC is the most valid method, determining the diagnosis earlier after surgery and at a lower lymphedema relative volume than WDM (Study I).
- Both TDC method and WDM could detect changes in mild BCRL over a six month-period of standard treatment, but the methods measure different aspects of lymphedema and need to be interpreted separately (Study II).
- Immediate treatment with a compression garment could prevent progression of mild BCRL, showing smaller proportions of progression in LRV, larger reduction in LRV and local tissue water, and reduced experience of tension, compared to no compression garment. However, 43% in the non-compression group did not show progression and could manage without compression garment (Study III).
- The participants with mild BCRL experienced a high overall HRQOL, but the participants wearing compression garment experienced a higher negative impact on HRQOL in the practical domain and in some psychosocial items, compared to those not wearing compression garment. The minor negative impact on HRQOL, when using compression garment needs to be considered in relation to the preventive effect (Study IV).

Clinical implications

- The results in this thesis have important clinical implications for early diagnosis, treatment, and HRQOL in women with mild BCRL, but also when it comes to clinical decision making, patient education and planning of future studies.
- It is import with regular follow ups/screening in a surveillance program for early mild BCRL during the cancer treatment, because women with mild BCRL do not necessarily have subjective symptoms in the arm and may not be attentive to onset of lymphedema.
- The use of TDC in combination with WDM and skin palpation for diagnosis of early mild BCRL is recommended. It is appropriate to measure with TDC at the medial site of the arm, proximal and distal of the antecubital fossa and at other measuring sites where you can palpate an increased skin and subcutaneous thickness.
- Both TDC and WDM can be used for evaluation of compression treatment in mild BCRL. However, the methods should be interpreted separately because the methods measure different aspects of lymphedema. It is recommended to follow several sites, above thresholds at start of treatment. The medial sites in the upper arm and forearm near the antecubital fossa are most appropriate to follow.
- Immediate treatment with compression garment is recommended because it reduces the risk of progression in LRV, but also decrease LRV, local tissue water and perceived tension in the arm. However, many patients with mild BCRL may also manage without compression. If the patient chose not to wear compression garment, it is important with follow up visits within 3 months of diagnosis when the risk of progression is greatest.
- Preventive prescription of compression garments to all patients treated with ALND is not recommended, because the incidence of BCRL is about 40% (30) and of these 43% are expected to have no progression in lymphedema volume, without compression treatment (paper III). (Of all patients treated with ALND, 23% would have benefit and 77 % would not).
- The women who used compression garment had a higher negative impact on HRQOL in the practical domain, and in some of the psychosocial items. Therefore, the use of compression garment needs to be evaluated regularly and the effect should be considered in light of the patient's perceived discomfort or problem of using compression. It is important to discuss physical, psychological, and practical issues related to the lymphedema, individual and in group-education to improve HRQOL.

Future research and perspective

- The TDC method can be used to detect/diagnose mild BCRL (paper I) and was shown to be able to detect changes during standard treatment (paper II). However, these changes in local tissue water may be due to an attempt to reroute the lymph flow after the ALND and therefore we do not know if the TDC method is a good predictor for persistent BCRL or not. Future research is needed to examine its use in evaluation of treatment and predictive value.
- The TDC method was the most valid method to detect mild BCRL, but the WDM method was also needed. Future prospective studies may show if TDC alone can diagnose mild BCRL at an early stage or if a combination with WDM is needed.
- It was most appropriate to measure with TDC at the medial sites in the arm (paper I, II). Previous studies on TDC thresholds for diagnosing lymphedema are based on moderate/severe arm lymphedema and with measuring sites ventral on the arm. To further improve diagnosis of early mild BCRL, studies examining the normal variations in local tissue water (TDC) in women with mild BCRL during cancer treatment and with measurements at the medial sites are needed. Also, to improve evaluation, interpretation of treatment results, and counselling, studies showing if and how the local tissue water is changed shortly after physical activity/exercise, or compression treatment are needed.
- Treatment with compression garment for 6 months prevented progression in LRV (paper III). However, future studies are needed to examine the long-term effects of this intervention and examine the effect of interventions with different durations (for example 12 months).
- Forty-three percent of the participants in the NCG had no progression and did not need to use compression garment (paper III). However, the results did not tell which participants who did not have progression. Thus, studies are needed to investigate which factors that are related to the regression/progression of mild BCRL.
- Women with mild BCRL experienced a high HRQOL, measured with LyQLI (paper IV). Future studies are needed to examine disease specific HRQOL with LyQLI in women with moderate/severe BCRL, to be able to compare results in the domains and specific items.

- Overall, international consensus about diagnostic methods and thresholds for diagnosis and intervention in early mild BCRL are needed. A consensus would make it possible to compare research results and facilitate future research in the area.
- Traditional treatment of lymphedema consists of several components included in the Complex Decongestive Therapy (CDT). The components are education/counselling in self-care (physical exercise, weight control and skin care), Manual Lymph Drainage (MLD), bandaging and prescription of a compression garment. Sometimes additional treatment with Intermittent Pneumatic Compression (IPC), laser therapy or other treatments also can be given, which makes it difficult to determine which treatments the patient benefits from. In the future, it is necessary to assess the effectiveness of each individual component to be able to individualize the treatment, which may improve patient outcomes and better adherence by the patient.

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About the author

Early diagnosis and treatment of Breast Cancer Related Lymphedema (BCRL) is important to prevent progress and negative impact on Health-Related Quality of Life (HRQOL).This thesis evaluted methods for early diagnosis, treatment and HRQOL in women with mild BCRL. Katarina Blom is a physiotherapist and lymphedema therapist and she has a long experience in cancer rehabilitation and treatment of patients with lymphedema.

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