Physical Therapy Reviews

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yptr20

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To cite this article: Karin Johansson , Katarzyna Ochalek & Sandi Hayes (2020): Prevention of arm lymphedema through the use of compression sleeves following breast cancer: results from a targeted literature review, Physical Therapy Reviews, DOI: 10.1080/10833196.2020.1822140

To link to this article: https://doi.org/10.1080/10833196.2020.1822140

Published online: 10 Oct 2020.

PHYSICAL THERAPY REVIEWS
https://doi.org/10.1080/10833196.2020.1822140

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Prevention of arm lymphedema through the use of compression sleeves following breast cancer: results from a targeted literature review

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ABSTRACT

Background: Breast cancer-related lymphedema (BCRL) is associated with impaired function and poorer quality of life. BCRL is also considered time-consuming and costly to treat. While compression treatment is considered the most efficient and effective form of treatment for early BCRL, its impact on the lymphatic system highlights its potential in the prevention of lymphedema.

Objectives: To identify and summarise studies evaluating compression garment as a prevention strategy for BCRL.

Methods: This is a targeted literature review of studies that evaluated use of compression garment in the prevention of BCRL, including prevention post-surgery and prevention of progression of subclinical lymphedema.

Results: A total of 4 studies were identified that assessed the role of compression garment in the secondary (one randomized, controlled trial; $n = 45$) or tertiary (three cohort studies; sample size range: 111–508) prevention of BCRL. Together, findings from these studies suggest that use of compression garment was associated with reduced incidence, attenuation of lymphedema or prevention of progression to more severe lymphedema. However, the absence of a randomized, controlled trial in the tertiary setting means causal inferences relationship cannot be made.

Conclusion: There is significant scope for further research, with consideration of possible benefits and costs associated with differences in compression class, duration or daily wear time, as well as comparison to other preventive strategies including patient preferences.

KEYWORDS
Breast cancer; lymphedema; prevention; compression

Background

Each year, more than 1.7 million new cases of breast cancer will be diagnosed worldwide, making breast cancer the most common cancer in women [1]. In many countries with advanced medical care, the five-year survival rate of early stage breast cancers is 80–90 per cent [1]. However, the personal and societal impact of the morbidity associated with the disease and its treatment is significant, adversely influencing the lives of women well beyond their diagnosis. Ranking high among breast cancer survivorship concerns is lymphedema of the arm, breast and/or chest, that is, breast cancer-related lymphedema (BCRL). High body mass index, more extensive surgery, such as mastectomy, and more extensive axillary lymph node dissection (ALND) have strong evidence as risk factors for the development of BCRL [2]. While ALND with radiotherapy has traditionally been shown as a 'significant' risk factor [3], with a relative risk of 1.9 [4], more recent evidence also supports receipt of chemotherapy as a risk factor. Findings from prospective surveillance studies collecting data up to 10 years post-diagnosis, report persistent lymphedema incidence at 30–40% for women with risk factors [3,5,6].

The lymph stasis in lymphedema starts an inflammatory process [7] in the subcutaneous tissue leading to early (potentially within the first year) deposition of fat [8], including intramuscular fat [9,10], which then adversely influences the lymph system, contributing to further increases in swelling. Since lymphedema, that is characterised by increased fat deposition with or without pitting, is time-consuming and costly to treat, it is of great importance to prevent the development of lymphedema. As such, understanding how best to prevent lymphedema has significant potential to reduce breast cancer-related morbidity and costs.

Primary prevention of lymphedema relates to avoiding injury to the lymphatic system to a level whereby risk of BCRL increases. This has at least partly been achieved by replacing axillary node

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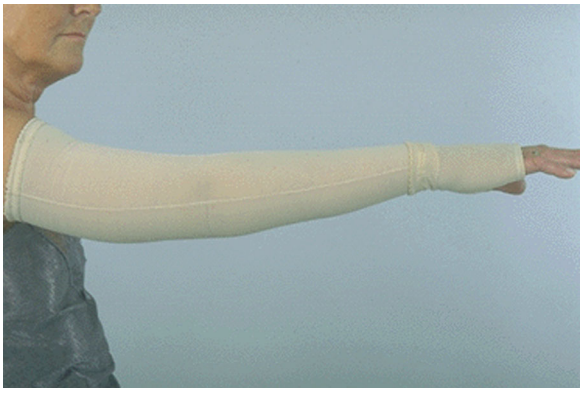

Figure 1. Compression sleeve with glove (Photo K. Johansson).

sampling (random sampling of typically >10 axillary lymph nodes) with sentinel node biopsy (SLNB) whereby 1–3 specific lymph nodes are sampled, as well as through the use of more targeted radiotherapy, whereby treatment is only given to the breast area and not to the axilla. For those receiving SLNB, incidence of BCRL is considered low (5%) [2]. However, when there is evidence of disease in sentinel nodes, more extensive ALND follows, typically alongside additional radiotherapy to the axilla. In these patients, primary prevention by avoiding injury to the lymphatic system by cancer treatment is not possible. *Secondary prevention* of lymphedema relates to prospective monitoring of patients at risk for the purpose of early identification of lymphedema, with or without modification to other potential factors, that could ultimately protect or support lymphatic function. As lymphedema is considered a chronic, generally incurable condition, requiring lifelong care [11], *tertiary prevention* in this context relates to implementing strategies or treatments that may reduce the impact, prevent progression or aid management of this condition. Lymphedema is considered the most feared sequelae following breast cancer, and its subsequent impact on function, social and psychological wellbeing is significant [11]. As such, identifying effective prevention strategies is of clear importance to women with breast cancer. Compression treatment (Figure 1) is considered the most efficient and effective form of treatment for BCRL [12,13] and its use has been associated with improvements in important quality-of-life parameters [14].

Although not fully elucidated, compression may support the lymphatic system through prevention of fluid accumulation in the compressed area and/or through encouragement of lymphatic drainage. It is therefore also plausible that compression may have an important role in secondary and tertiary prevention of BCRL. Thus, the aim of this review was to compile the evidence on compression garment intervention for prevention of BCRL.

Method

A targeted literature review [15] was undertaken to identify studies evaluating compression garment as a secondary or tertiary prevention strategy for BCRL published prior to 1st May, 2020, and to provide a summary of their findings. The conduct of the review was largely based on a knowledgeable selection of relevant articles, and a manual search of the reference lists from those articles. Nonetheless, the procedure was also supported by a search in PubMed, CINAHL, Cochrane, Embase and Pedro, applying the key words prevention, lymphedema, AND compression. While this last search used broad search terms, it did not reveal any other papers not already known.

Selection

Participants

Studies involving participants treated for breast cancer with SLNB or ALND or radiotherapy.

Interventions

Studies that evaluated the effect of any form or grade of compression garment on secondary OR tertiary prevention, with application of compression garment therapy immediately after surgery (secondary prevention) or following diagnosis of subclinical lymphedema (tertiary prevention), for a minimum intervention duration of four weeks. Subclinical lymphedema can be defined as ≥3% increase of arm volume compared to preoperative measurements [16] or as lymphedema relative volume (LRV, percentage difference between healthy and edematous arm) ≥5% [17].

Comparators

Single-group studies, and studies comparing compression garment therapy with no compression garment (usual care). Usual care may or may not include exercise, self-massage, weight control and/or skin care activities.

Outcomes

Included studies must have evaluated lymphedema using objective measurements of total arm volume or excess volume, bioimpedance spectroscopy (BIS) or tissue dielectric constant (TDC).

All identified articles using the search strategy were identified by KJ and KO. All included studies have used parametric tests for comparison and data are presented as means ± standard deviation.

Table 1. Studies evaluating the effect of compression in the secondary or tertiary prevention of breast cancer-related arm lymphedema.

Study	Study design	Sample size (n)/ groups	LE measurement method/LE definition	Garment/time	Results
Secondary prevention					
Ochalek et al. [18]	RCT	45 IG = 23 CG = 22	Calculation of arm volume by circumferential measurements Increase compared to pre-surgery Subclinical LE ≥ 5% – < 10% LE ≥ 10% LE	Sleeve, ccl 1/ 2 years	Arm volume change 3 mo: IG −24 ml CG +57 ml 12 mo: IG –68 ml CG +115 ml Percentage with LE 1 year: IG 17% CG 27% 2 years: IG 15% CG 29%
Tertiary prevention					
Stout Gergich et al. [16]	Case-control	IG = 43 with LE CG = 43 no LE	Arm volume by Perometer/Increase compared to pre-surgery Subclinical LE ≥3%	Sleeve, ccl 2/ Mean 4.4 weeks	Percentage arm volume change Mean 4.8 mo: IG −4.1% CG none
Johansson and Branje [5]	Retrospective	98	Arm volume by water displacement method/LE; increased thickness of subcutis compared to healthy side and ILD ≥ 5%	Sleeve, ccl2/ Mean 48.9 mo	ILD Baseline 8.1% 48.9 mo 9.0% Percentage with ILD <5% 26.5% ≥5% – <20% 60.2% ≥20% 13.3%
Ridner et al. [19]	RCT	BIS 41 TM 68	BIS/ LE; increased ≥ 10 L-Dex units TM: Calculation of arm volume by circumferential measurements / LE; ≥ 10% increase from pre-surg	Sleeve, ccl 2/ 4 weeks	Percentage with no increase in LE BIS: 95% TM: 85%

Abbreviations: LE, lymphedema; RCT, randomized controlled trail; IG, intervention group; CG, control group; ILD, interlimb difference; BIS, bioimpedance spectroscopy, TM, tape measurements; ccl, compression class 1 = 15–20 mmHg, ccl 2 = 23–32 mmHg.

Results

A total of 4 studies that assessed the role of compression garment in the secondary ($n = 1$) or tertiary ($n = 3$) prevention of BCRL were included (Table 1). Study designs included one randomized, controlled trial ($n = 45$) and three cohort studies (sample size range: 111–508). A more detailed summary of key design features and subsequent findings of these included studies follows.

Secondary prevention

In a randomized, controlled trial [18] of 45 women treated for unilateral breast cancer with SLNB ($n = 24$) or ALND ($n = 21$), and radiotherapy, the use of daily compression garment, starting immediately after surgery and continuing for 12 months post-surgery was compared against usual care. The intervention group (IG, $n = 23$) wore compression sleeves in compression class (ccl) 1 (15–21 mmHg), and was advised to participate in daily upper-body mobility exercise for 15 min. The control group (CG , $n = 22$) was also advised to participate in the daily exercise routine, but without daily use of compression sleeves. While there was no statistical significance in baseline arm volume measures between the IG and CG, body mass index was higher for those in the CG (28 vs 25.6) and the proportion of those undertaking ALND was higher in the IG versus the CG (61% vs 32%). All participants had limb volumes for both arms measured before surgery and at one, three, six, nine, and 12 months post-surgery, *via* circumferential measurements. An arm volume increase exceeding 10%, compared with pre-surgery volume, was defined as lymphedema. Differences of >5% in the first postoperative month was considered subclinical lymphedema and was found in four patients in the IG and three in the CG. At three months post-surgery, the IG showed significantly lower mean arm volumes in the affected arm when compared with arm volumes for those in the CG (−23.7 ml vs 57.2 ml), with the difference increasing in favour of those wearing compression sleeves (i.e. the IG) by 12 months post-surgery (−67.6 ml vs 114.9 ml). At one and two-years post-surgery, lymphedema was evident in 17% and 15% for those wearing compression sleeves, respectively, versus 27% and 29% for those who did not wear compression sleeves [14]. Consequently,

the results from this study suggest that use of compression alongside daily mobility exercises may be an effective form of secondary lymphedema prevention.

Tertiary prevention

A case-control study of the use of compression sleeve treatment for subclinical arm lymphedema was embedded within a prospective, surveillance study, designed to assess breast cancer treatment-related morbidity (including lymphedema) in 196 women with newly diagnosed, unilateral breast cancer [16]. Participants were assessed preoperatively and at one, three, six, nine, 12 and 18 months post-operatively. Subclinical BCRL was predefined as a volume increase of $\geq$3% in the affected arm compared with the patient's preoperative measurement and was identified in 43 patients. On detection of subclinical BCRL, these women were provided with compression sleeves (ccl 2, 23–32 mmHg) for daily wear for 4 weeks. If arm volume had reduced below the subclinical threshold on follow-up, participants were advised to only wear the garment during strenuous activity, with symptoms of heaviness, or with visible swelling. For those whose volume remained above the threshold, continued daily wear of compression sleeves was advised. Subclinical BCRL was diagnosed on average at 6.9 months post-operatively, with a volume increase of the affected arm of 6.5 ± 9.9%. The mean duration of the compression intervention was 4.4 ± 2.9 weeks, following which a volume decrease of 4.1 ± 8.8% was observed at an average follow-up of 4.8 months. For comparison, an age-matched control group ($n = 43$) of women without BCRL was selected from the study sample, with no changes in arm volume identified in this sub-group over time.

In a retrospective study of 292 women treated for unilateral breast cancer with ALND and radiotherapy, followed for up to 10 years post-surgery with twice yearly lymphedema assessment, 39% ($n = 111$) were found to have BCRL defined as increased thickness of subcutis and inter limb difference $\geq$5% [5]. Immediately following lymphedema diagnosis, women were educated in self-care and supplied with compression sleeve ccl 2, which was renewed at each assessment occasion. Of the 111 women with lymphedema, 13 were excluded from further analyses as two were found to have preoperative lymphedema and a further 11 patients were diagnosed with recurrent disease within one-year of lymphedema diagnosis. Data from the remaining 98 women were used in subsequent analyses. Mean time of lymphedema diagnosis was 11.5 ± 12.8 months post-surgery and mean LRV at time of diagnosis was 8.1 ± 3.6%. At time of last available follow up measurement (48.9 ± 39.2 months post-surgery) there was no significant change in mean LRV (9.0 ± 6.7%). Further, for the majority of women (86.7%) compression sleeve treatment was associated with attenuation of lymphedema (i.e. for 26.5% LRV was below 5%) or maintenance of mild to moderate lymphedema (i.e. for 60.2% LRV was below 20%). However, for 13.3%, compression sleeve was insufficient as their LRV exceeded 20% and required more intensive lymphedema treatment.

Recent findings from a randomized, controlled trial ($n = 508$) evaluating the effect of prospective lymphedema surveillance on lymphedema incidence, comparing the use of bioimpedance spectroscopy (BIS) versus tape measure (TM) to investigate early lymphedema treatment (compression sleeve) also provide some insight into the potential role of compression as tertiary prevention [19]. This trial implemented compression sleeves for a minimum of 4 weeks for those women whose BIS or TM measurements exceeded their preclinical lymphedema threshold. Compression sleeve was sufficient for treatment or prevention of progression for 95% and 85% of women in the BIS and TM group, respectively. The remaining 5% and 15%, respectively, continued to show progression of their lymphedema and required treatment of complex decongestive physiotherapy.

Discussion

This is a targeted literature review, summarizing the key features of four studies evaluating the role of compression garment in the secondary and tertiary prevention of BCRL. Findings from one small, randomized, controlled trial suggest potential benefit through the use of compression garment in the prevention of BCRL, amelioration of preclinical or early lymphedema and prevention of progression to lymphedema requiring more complex and time-consuming treatment. While studies assessing compression garment in tertiary prevention reported findings in favor of compression use, study design precludes the ability to determine cause and effect.

While findings are supportive of compression garment in secondary and tertiary lymphedema prevention, limitations of the current evidence-base however need to be acknowledged. First, only one secondary prevention study has been conducted. While this study was a randomized, controlled trial, sample size was small and the baseline imbalances between the compression and control group in key lymphedema risk factors, including body mass index and extent of lymph node dissection, may have influenced findings. Second, in the evaluation of compression garment in

tertiary prevention, the evidence base is supported only by cohort studies, one of which was retrospective in design. Consequently, causal relationships cannot be determined by findings from these studies. That is, it is plausible that the declines in lymphedema outcomes observed with compression use could have happened in the absence of compression. Recently, these theories were supported by Gençay Can et al. [20], who found a reduction of LRV from 7,2% to 4,4% in patients ($n = 25$) with subclinical BCRL, taking part in a one-month program, including self-care and mobility exercise, but no compression treatment. Further, findings from previous population-based breast cancer cohort studies, which have measured lymphedema status but not intervened, also support this possibility. Specifically, it has been identified that while lymphedema is considered a chronic condition, for some, lymphedema is acute (present for $<$ 3 months) and may subside in the absence of treatment [21,22]. The included studies also highlight the need for reliable measurements and definitions of subclinical lymphedema. Both percentage increase compared to pre-surgery measurements [16,18,19] as well as increase in volume difference between the limbs were applied [5]. However, by long-term follow-up volume difference between the limbs always has to be taken into account, due to body weight change and thereby normal change of limb volume. Finally, study samples were typically advised or encouraged to participate in daily upper-body mobility exercises (making it difficult to fully attribute study findings to compression alone) and reporting of adherence and compliance data to compression and/or mobility exercises was lacking.

Although significant limitations exist to the extent to which current secondary and tertiary lymphedema prevention studies can be used to guide practice, overall their findings are consistently positive (in favor of compression garment) and as such, provide the necessary pilot data for the design and conduct of future randomized, controlled trials. One such trial is already underway [23]. Specifically, women with subclinical lymphedema ($n = 75$) were invited to participate in a study which compares no compression sleeve treatment ($n = 38$) with daily compression sleeve (ccl 1; $n = 37$) for 6 months. Subclinical arm lymphedema was defined as LRV 5–8% and/or a tissue dielectric constant (TDC) of 1.3–1.45. While the primary findings are currently being analyzed, recruitment and retention data suggest class 1 compression in the early treatment of lymphedema is appealing to women (78% of eligible women agreed to participate), is safe (no adverse events have been reported by those in the compression group) and is feasible (<1% withdrawal rate). Also, the adherence in the compression group was good, with all patients wearing the compression sleeve for 6 months (12% half the day and 88% more than eight hours a day). While findings from this trial will provide important contributions to the evidence in support or refute of compression sleeve in tertiary lymphedema prevention there remains significant scope for additional research in this area. For example, the effect of differences in compression class, duration or daily wear time of compression represents areas in need of future investigation. Also, understanding the effect of compression versus other forms of prevention strategies (e.g. manual lymph drainage, upper-body mobility exercise, whole-body exercise, etc), cost-effectiveness of secondary versus tertiary prevention through compression (acknowledging that tertiary prevention would require prospective surveillance and associated costs) and patient preferences related to compression garment versus other forms of treatment will be important for influencing widespread patient care.

Conclusion

While the preliminary evidence is supportive of compression garment as a secondary or tertiary prevention strategy, the current body of evidence is insufficient to guide clinical practice. Instead, additional research is needed in this area, including the examination of the effect of differences in compression class, duration or daily wear time, as well as comparison of compression garment with other preventive strategies that consider patient preferences that may or may not be associated with age, mobility issues and patient engagement.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

No internal or external funding was received for preparing the manuscript.

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