Review Article

Conservative and Dietary Interventions for Cancer-Related Lymphedema

A Systematic Review and Meta-Analysis

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The findings support the use of compression garments and compression bandaging for reducing lymphedema volume in upper and lower extremity cancer-related lymphedema. Specific to breast cancer, a statistically significant, clinically small beneficial effect was found from the addition of manual lymph drainage massage to compression therapy for upper extremity lymphedema volume. ***Cancer* 2011;117:1136–48.** © *2010 American Cancer Society*.

KEYWORDS: cancer-related lymphedema, dietary interventions, conservative interventions, manual lymph drainage.

Lymphedema remains a prevalent and potentially debilitating side effect of cancer treatment. Although data on the prevalence of lymphedema are limited, it is estimated that over 3 million people in the United States suffer from lymphedema, with a significant proportion developing the disease secondary to cancer and/or cancer treatment.[1] When treated conservatively in the earliest stages, complications of lymphedema may be diminished or reversed.[2] Unfortunately, lymphedema may progress to irreversible swelling and fibrosis requiring lifelong attention and management.[1,3,4] Thus, the impact of chronic lymphedema for the cancer survivor is often profound, resulting in significant psychosocial morbidity and poorer quality of life.[5,6]

The effectiveness of conservative interventions for lymphedema has been assessed in several systematic reviews; however, these reviews have been limited in scope.[7,8] Kligman et al performed a systematic review of randomized controlled trials (RCTs) examining conservative and medical therapies for breast cancer related lymphedema.[7] This review included 10 studies examining both conservative (6 studies) and medical therapies (4 studies) for lymphedema. The authors reported positive findings from use of a compression garment, early evidence in support of pneumatic compression pumps, and conflicting/no evidence for medical therapies. Moseley et al performed a systematic review examining the effect of conservative therapies for breast cancer related lymphedema.[8] The review included 43 trials examining conservative and pharmacological interventions that included randomized and controlled clinical trials, as well as case control and cohort studies. In contrast to the Kligman review, the authors concluded that all conservative therapies produced improvements in upper extremity lymphedema volume, with more intensive therapies resulting in greater volume reductions.[8] It is known, however, that the inclusion of nonrandomized and uncontrolled trials may result in an overestimate of treatment effect[9]; therefore, it is recommended that systematic reviews be limited to RCTs whenever possible. The aim of this systematic review was to update the evidence from RCTs concerning the benefits of conservative and dietary interventions for all cancer-related lymphedema.

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The authors acknowledge Huseyin Oylupinar, PhDc, Department of Modern Languages and Cultural Studies, University of Alberta, for his assistance with language translation.

DOI: 10.1002/cncr.25513, **Received:** February 20, 2010; **Revised:** May 24, 2010; **Accepted:** June 1, 2010, **Published online** November 8, 2010 in Wiley Online Library (wileyonlinelibrary.com)

MATERIALS AND METHODS

We searched the following electronic databases from January 1980 to August 2009: MEDLINE, PubMed, EMBASE, CINAHL, Dissertation Abstracts, PEDro, and EBM Reviews (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews). We used search terms related to cancer (eg, neoplasms, axillary dissection, lymph node excision), lymphedema (lymphedema, lymphoedema, edema), conservative treatments (stockings, compression, manual lymph drainage), and publication type (random allocation, clinical trial). Published and unpublished studies were considered with no language restrictions. To locate unpublished research, we reviewed proceedings from lymphedema conferences and clinical practice guidelines for cancer. We also searched websites housing clinical trial details, theses, or dissertations. In addition, we hand-searched the reference lists of all potentially relevant studies and contacted experts to identify relevant articles.

Criteria for Considering Studies for This Review

Studies were considered eligible for inclusion if they were RCTs examining the effectiveness of a conservative or dietary intervention to a placebo, control, or comparison intervention (Table 1). Trials were included if they involved adult participants with secondary lymphedema from cancer. Studies including noncancer-related participants were considered for inclusion, providing >80% of the sample was composed of secondary lymphedema from cancer. The primary outcome of interest was change in lymphedema volume (eg, percent reduction, absolute volume reduction in milliliters). Secondary outcomes of interest included quality of life, function, and lymphedema symptoms (pain, tension, heaviness, discomfort). Information was sought on adverse events of interventions.

One reviewer (MLM) performed the initial search of all the databases to identify potential trials and screened the results to exclude articles that were clearly irrelevant. Two independent reviewers (MLM and CJP), using the defined eligibility criteria, screened for trial inclusion. A priori, reviewers made the decision to exclude any data that were available only in abstract form. Results at each stage were compared and disagreements resolved by consensus. Where necessary, a third reviewer (JLY) was used to resolve any disagreements.

Table 1. Interventions Considered for Inclusion

Compression garment (CG)
Compression bandaging (CB)
Compression systems: specialized garments
Electrophysical modalities (eg, low level laser therapy, electrical stimulation)
Elevation
Exercise
Intermittent pneumatic compression (IPC) pumps
Manual lymph drainage (MLD) massage
Self-massage (SM) techniques
Decongestive lymphatic therapy (DLT)
Dietary/weight loss intervention

Methodological Quality Assessment

Assessments of quality were completed independently by 2 reviewers (MLM and CJP). Each study was evaluated using a modified version of the previously validated Jadad 5-point scale to assess randomization, blinding, and withdrawals/dropouts.[10] In these studies, however, double blinding is not always possible (ie, participants may know the treatment they are receiving). Therefore, quality was summarized using a modification of the Jadad scoring system as follows: 1) Was the study described as randomized?; 2) Was the method of randomization adequate?; 3) Was there adequate concealment of allocation?; 4) Was the outcome assessment described as blinded?; 5) Was there a description of withdrawals and dropouts? Studies were defined as "high" quality if they fulfilled 3 or more quality criteria.

Data Analysis

Study results were pooled, if appropriate, using random effects models after heterogeneity among the trials was considered. Trials were combined using Comprehensive Meta-Analysis by Biostat. Continuous data that were the products of several different scales or methods were summarized as the standardized mean difference (SMD). All similar studies were pooled and point estimates reported with their associated 95% confidence intervals (CI). Heterogeneity was assessed using a chi-square test that considered a *P*-value of less than .10 to indicate significant heterogeneity. I-squared values were also calculated to quantify variability in study effect. Recommended cut-points for i-squared values of 25%, 50%, and 75% were used to describe low, moderate, and high heterogeneity, respectively.[11]

Where pooling was not possible or appropriate, a qualitative analysis was conducted based on the following rating system[12]:

Level 1, strong evidence: generally consistent findings in multiple high-quality trials.
Level 2, moderate evidence: generally consistent findings in multiple low-quality trials and/or 1 high-quality trial.
Level 3, limited evidence: only 1 low-quality trial.
Level 3b, conflicting evidence: inconsistent findings in multiple trials.
Level 4, no evidence: no RCTs.

RESULTS

We identified 157 papers, of which 48 were considered potentially relevant. Independent review of these 48 papers led to the inclusion of 25 studies involving 1018 participants.[13-37] Studies were carried out in 14 different countries/regions worldwide. Study methodology varied significantly, particularly in regard to the chosen intervention and comparison treatment (Table 2). Of the included studies, 2 authors provided additional information on study methods[16,18] and 1 author provided additional data for use in the meta-analysis.[18] Kappa statistics for agreement between the reviewers on inclusion of trials and quality score was 0.7 and 0.9, respectively.

Only 8 of 25 studies met the criteria for high quality (Table 3). The most common methodological shortcomings in the included studies were method of randomization not described/appropriate (19 studies scored "negative" or "unclear"), inadequate concealment of allocation (22 studies scored "negative" or "unclear"), and failure to blind the outcome assessment (20 studies scored "negative" or "unclear").

Meta-analysis was only possible for studies examining the additional effect of manual lymph drainage (MLD) for the outcome of upper extremity lymphedema volume in breast cancer survivors. Heterogeneity precluded pooling of studies for other interventions and outcomes. Therefore, qualitative analyses were performed for the remaining interventions (Table 4) and endpoints (Table 5).

Quantitative Analysis

Five studies[13,18,28,33,37] involving 198 patients examined the benefit of the addition of MLD to compression therapy (+/− other treatments) compared with compression therapy (+/− other treatments) alone. The pooled results demonstrated a statistically significant benefit from the addition of manual lymph drainage (SMD: 0.37; 95% CI, 0.07 to 0.67; $P = .02$) for reducing upper extremity lymphedema volume (Fig. 1). In the analysis, no significant statistical heterogeneity was identified ($P = .36$), and the i-squared value of 14% indicated low variability among studies. No evidence of benefit from MLD was found for lymphedema symptoms of pain, tension, heaviness, or QoL.

Level 1 Evidence (Strong Evidence)

The strongest qualitative evidence came from 3 studies,[27,31,35] totaling 203 participants, that examined the effect of exercise on upper extremity lymphedema volume in breast cancer. Whereas exercise was not found to improve or exacerbate existing upper extremity lymphedema volume, significant benefit was found for lymphedema symptoms of pain/tenderness[31] and quality of life.[27,35]

Level 2 Evidence (Moderate Evidence)

Three studies[16,20,21] with 109 participants showed improvement in lymphedema volume with use of a CG. All 3 studies reported benefit from CG, with 2 studies reaching statistical significance.[16,20] In 1 study[16] with Kaposi sarcoma survivors, daytime use of a CG was found to be significantly better than no-treatment. In the second study[20] with breast cancer survivors, daily CG, prescribed in conjunction with exercise and self-massage, was significantly better than exercise and self-massage alone. These 3 studies provide evidence of benefit from a CG for both upper and lower extremity lymphedema and for survivors of breast cancer and Kaposi's sarcoma, respectively.

Evidence for CB was demonstrated in a single high-quality trial[14] including 90 participants. In the study, benefit was found after 18 days of CB (followed by maintenance with a CG) when compared with use of CG alone. Benefit from CB was seen for both upper and lower extremity lymphedema immediately after the intervention and at 24-week follow-up.

In another single high quality study[32] with 24 breast cancer survivors, a 12-week dietary intervention focusing on weight loss resulted in a significant reduction in upper extremity lymphedema volume. In the study, women in the intervention group were advised to reduce their caloric intake to between 1000 and 1200 kilocalories per day. The women lost on average 3.3 kg (± 2.6) of body weight

Table 2. Characteristics of Included Studies

Study	Sample Size/Population	Experimental Treatment n=number analyzed	Comparison/ Control Treatment n=number analyzed	Relevant Outcomes	Results
Andersen, 2000 Denmark	N=44 Breast cancer Median age: 53 y	n=20 MLD: 8x over 2 wks SM, compression garment, exercise & education - for 3 mo	n=22 Compression garment, exercise & education for 3 mo	Circumference into calculated limb volume Symptoms: discomfort, heaviness, pain, tightness, function, aching, mobility Adherence to treatment	48% MLD & CG; 60% CG: no significant difference between groups at 3 mo, $P=.66$ No significant difference between groups in other outcomes
Badger, 2000 United Kingdom	N=90 Mixed cancers: type not stated Upper & lower extremity LE Mean age: 57.4 y	n=32 CB for 18 d followed by CG for total of 24 wks & standard care	n=46 CG alone for 24 wks Standard care: education, self-massage & skin care	Limb volume using Perometer	CB & CG group: 31%; CG alone: 15.8%: significant difference between groups $P=.001$
Bertelli, 1991 Italy	N=74 Breast cancer Mean age: 64 y	n=37 Electrically stimulated lymphatic drainage 5x per wk for 2 wks, repeated after 5 wk break CG: 6 h/d	n=37 CG: 6 h per d; 9 wks	Circumference measured at 7 points along the arm	Mean reduction of 17% in both groups: no significant difference between groups
Brambilla, 2006[a] Italy	N=65 Kaposi sarcoma Lower extremity (unilateral) below knee Mean age: 71.7 y	n=50 Below knee compression stockings: 40 mmHg; worn from morning to bedtime for 15 mo Replaced stockings at 6 mo	n=15 No treatment control group for 15 mo	Circumferences at intervals of 1.5 cm calculated into limb volume	30/50 subjects in experimental group had reduction; 20/50 had an increase in volume Increase in volume in all control subjects Significant difference between groups in favor of compression-stocking group ($P<.001$)
Carati, 2003 Australia	N=61 Breast cancer Mean age: 64 y	n=26 Low-level laser: block 8 treatments followed by 8 wk rest; second block 8 treatments	n=27 Sham laser: block 8 treatments, followed by 8 wk rest; single block of 8 treatments	Limb volume using Perometer Bioimpedence Tonometry Symptoms QoL	No significant difference between placebo &1 cycle of laser or when comparing single cycle to 2 cycles of laser for RCT portion of trial NB: Follow-up data include pooling of subjects from cross-over (not RCT)
Didem, 2005[a] Turkey	N=56 Breast cancer Mean age: 54 y	n=27 DLT: MLD, CB, exercise & skin care, self-massage, walking: 3 d/wk for 4 wks	n=26 SP: CB, elevation, exercises, skin care, self-massage, walking: 3 d/wk for 4 wk	Circumference Limb volume using water displacement	DLT: 55% reduction; SP: 36% reduction: significant difference $P<.05$ No significant difference between groups for shoulder range-of-motion outcome
Dini, 1998 Italy	N=80 Breast cancer Mean age:62 y	n=40 IPC (60 mmHg for 2 hours): 5x per wk for 2 wks, repeated after 5 wk break Skin care education	n=40 No treatment Skin care education only 9-wk period	Circumference measured at 7 points along arm	IPC: 25%; Control: 20% : no significant difference between groups

(Continued)

Table 2. (Continued)

Study	Sample Size/Population	Experimental Treatment n=number analyzed	Comparison/ Control Treatment n=number analyzed	Relevant Outcomes	Results
Hornsby, 1995 United Kingdom	N=25 Breast cancer Mean age: not stated	n=14 CG: worn 24 h Exercise Self-massage 4-28 wks	n=11 Exercise Self-massage 4-28 wks	Limb volume using water displacement	[b]CG: 24%; Control: -1%: Significant benefit in favor of compression garment in short term
Irdesel, 2007 Turkey	N=19 Breast cancer Mean age: 51.6 y	n=10 CG and exercise: CG: daytime use; Exercise: upper extremity ROM, light resistive exercises, bilateral/unilateral cane stretches, wall walking, pulleys Education & skin care	n=9 Exercise alone: as experimental group Education & skin care	Circumference Pain (VAS) Follow-up: 2 wk; 1, 3 & 6 mo	No significant between-group differences in measurements of circumference Pain & tenderness not analyzed as symptoms reported in only 1 subject; shoulder ROM not analyzed as restriction present in only1 subject
Jahr, 2008 Germany	N=22 Breast cancer n =20 & Melanoma n =1 Breast edema Mean age: 59.2 y	n=11 Deep oscillation & MLD; 12 sessions over 4-wk period; followed by MLD alone 1-2x per wk for 8 wks	n=10 MLD alone 1-2x per week for 12 wks	3D volume measurement of the breast Symptoms: pain, breast swelling	Significant reduction in pain score & decrease in subjective and objective breast swelling at 4-wk point. No significant differences between the groups at 8-wk follow-up (Week 12). NB: intervention group received more MLD treatments
Johansson, 1998 Sweden	N=24 Breast cancer Mean age: 61 y	N=12 Week 1-2: CG in daytime Week 3-4: MLD & CB (Vodder technique 45 min per session 5 d/wk for 2 wks)	N=12 Week 1-2: CG in daytime Week 3-4: Pneumatic pump 2 h/d at 40-60 mmHG 5 d/wk for 2 wks	Limb volume using water displacement Symptoms: heaviness, tension, pain	MLD & CB: 15% ; CB alone: 7%; no significant difference between groups No significant difference between groups for other outcomes
Kaviani, 2006 Iran	N=11 Breast cancer Mean age: 51.2 y	n=4 Low level laser therapy: Ga-As diode laser; 5 points to axilla; 3x/wk for 3 wks; 8 wk break; 3x/wk for 3 wks	n=4 Sham laser: same conditions as experimental group	Limb circumference Symptoms: pain, heaviness	No statistical analyses reported. Data presented in figure form without *P*-values
Kozanoglu, 2009 Turkey	N=50 Breast Cancer Mean age: 48.3 y	n=24 Pneumatic compression: 20 sessions over 4 wk period; 2 h duration/ session; pressure 60 mmHg Daily limb exercise, hygiene &skin care	n=23 Low level laser therapy: Ga-As laser device; 3 points antecubital fossa & 7 points to axilla; 12 sessions over 4 wk period (3x/wk) Parameters: 20 min/session; 904 nm, 2800 Hz, 1.5 J/cm2 Daily limb exercise, hygiene & skin care	Circumference Symptoms: pain, heaviness, tightness, paresthesia & weakness Measurements: baseline, post-treatment, 3, 6 & 12 mo	Significant differences between groups for circumference measurements at post-treatment, & 12 mo follow-up in favor of laser group Significant difference in change score for pain at 12 mo in favor of laser group

(Continued)

Table 2. (Continued)

Study	Sample Size/Population	Experimental Treatment n=number analyzed	Comparison/ Control Treatment n=number analyzed	Relevant Outcomes	Results
Maiya, 2008 India	N=20 Breast Cancer Mean age: not stated	n=10 Low level laser (He-Ne laser 632.8 mm and Diode laser 850 nm); at different points in axillary region, 2.4J/cm^2; duration 34 mins/d for 10 treatments. Upper extremity exercise program	n=10 Upper extremity exercise program: no details Compression garment	Circumference at 2 points: 15 cm proximal and 10 cm distal to lateral epicondyle Symptoms: pain	Baseline and change scores not provided. Inappropriate statistical analyses performed
McKenzie, 2003 Canada	N=16 Breast cancer Mean age: 56 y	n=7 Resistance exercise 3x/wk for 10 wks; arm ergometer 3x/wk for 8 wks starting after wk 2 plus CG	n=7 CG	Circumference Limb volume via water displacement QoL	No significant differences between exercise & control in arm circumference or arm volume Improvements in vitality (P=.048) and general health (P=.023) in favor of exercise group
McNeely, 2004 Canada	N=50 Randomized Breast cancer Mean age: 59 y	n=24 MLD+CB: Vodder 45 min, 5 d/wk for 4 weeks CB worn over weekend	n=21 CB: 5 d/wk for 4 wks CB worn over weekend	Circumference calculated into limb volume Limb volume via water displacement	MLD & CB: 46%; CB alone: 38.6%; no significant difference between groups, P=.217
Oliveira, 2008 Brazil	N=16 Breast cancer Mean age: 65.9 y	n=5 Physical therapy treatment: CDP(massage, Vodder method MLD, compression bandaging & skin care) 3x/wk for 4 wks plus daily diet therapy consisting of intake of medium chain triglycerides	n=5 Physical therapy treatment as per experimental group: 3x/ wk for 4 wks plus corn oil (placebo)	Limb volume: water displacement Bioimpedance: total body water Symtpoms: pain, discomfort & heaviness: VAS Body weight & height Dietary profile: food frequency questionnaire (daily, weekly, monthly), 24-h recall	Significant difference between the groups in volumetry measurement (MCT group reduction ~ 200 mL control group increase ~ 80 mL) and circumference of 10 cm below olecranon in favor of addition of MCT No significant differences were found for symptoms, total body water, or skinfolds
Radakovic, 1998 Kosovo	N=36 Breast cancer Mean age: 54.9 y	n=18 MLD & CB: 30 minutes/ session x 10 d	n=18 IPC & CB: 60 min/session x 10 d	Average reduction of arm circumference over 5 points along arm	Significant reduction in arm circumference in favor of IPC & CB (P<.05)
Schmitz, 2009 United States	N=141 Breast cancer Mean age exercisers = 56 y Mean (SD) control =59 y	n=71 1-y program: 13 wk group sessions; 90 min 2x/ wk. Upper body & lower body exercise program; little to no resistance for upper body, progressed repetitions and resistance within tolerance. Upper body exercise discontinued during any exacerbation of lymphedema	n=70 Participants asked not to change exercise behavior	Limb volume by water displacement Proportion with absolute increase of 5% or more in interlimb volume discrepancy Lymphedema exacerbations Symptoms Adherence	No significant difference in the proportion of women who had an increase in limb swelling of 5% or more between groups Significant improvement in symptoms (P=.03), upper body & lower body strength (both P<.001), and lower incidence of lymphedema exacerbations (P=.04)

(Continued)

Table 2. (Continued)

Study	Sample Size/Population	Experimental Treatment n=number analyzed	Comparison/ Control Treatment n=number analyzed	Relevant Outcomes	Results
Shaw, 2007 United Kingdom	N=24 Breast cancer Mean age: 60 y	n=11 Weight reduction diet: deficit of 1000 kcal per d & compression garment	n=10 Booklet of healthy eating & compression garment	Circumference measurements calculated into limb volume Height & weight Skin folds Dietary intake: 7-day dietary diary	Significant reduction in excess arm volume (reduction 349 mL or ~ 44%; $P=.003$), body weight (3.3 kg; $P=.02$), and BMI (1.3; $P=.016$) in favor of the weight-loss group
Sitzia, 2002 United Kingdom	N=28 Breast cancer Mean age: 71 y	N=15 MLD+CB: Leduc protocol, 90 min/d, 5 d/wk for 2 wks Series of exercises: elbow flexion; hand, wrist & finger movements	N=13 SM & CB: 30 min/d, 5 d per wk for 2 wks Series of exercises: elbow flexion; hand, wrist & finger movements	Arm circumference calculated into limb volume	MLD & CB: 34%; SM &CB: 22%; no significant difference between the groups ($P=.34$)
Szuba, 2002 United States	N=23 Breast cancer Mean age: 67 y	n=12 IPC & DLT 5x per wk for 2 wk	n=11 DLT alone 5x per wk for 2 wk	Limb volume via water displacement	IPC & DLT 45%; DLT alone 26%; ($P=.05$) after 2 wk IPC & DLT 30%; DLT alone 27%; no significant difference at Day 40 (follow-up)
Tidar, 2009 Israel	N=48 Breast cancer Mean age: 56 y	n=16 Aqua lymphatic therapy and self-management (as per control group)	n=32 Self-management: compression garment, self-massage and exercise	Limb volume via water displacement Adherence to treatment QoL Adverse events: eg, infection	No significant between-group difference in lymphedema volume Significant improvement in emotional and social dimensions of QoL in favor of Aqua Lymphatic Therapy
Wilburn, 2006 United States	N=10 Breast cancer Mean age: 60 y	n=5 Self-administered, Flexitouch mechanically stimulated MLD alone	n=5 CG & daily SM x 14 d	Circumference into calculated limb volume QoL	No between-group analysis performed for volume change in RCT portion of trial No significant differences in quality of life
Williams, 2002 United Kingdom	N=31 Breast cancer Mean age: 59.5 y	N=15 MLD & CG: Vodder technique, 45 min/d for 5 d for 3 wks, 6-wk break, 3 wks SM	N=16 SM: 20 min/d & CG for 5 d for 3 wks, 6-wk break, 3 wks MLD	Circumference calculated into limb volume Trunk volume (calipers) Dermal thickness (ultrasound) QoL Symptoms: VAS	No significant difference between groups in limb volume No significant between-group differences in other outcomes

ADL indicates activities of daily living; CB, compression bandaging; CG, compression garment; DLT, decongestive lymphatic therapy; IPC, intermittent pneumatic compression; MLD, manual lymph drainage; QoL, quality of life; RCT, randomized controlled trial; ROM, range of motion; RT, radiation therapy; SM, self-massage; SP, standard physiotherapy; VAS, visual analog scale.

[a] Unpublished information on methods and additional data provided by author.

[b] Analysis performed based on data provided in published paper.

Table 3. Methodological Quality of Included Trials

Study	Was the Study Described as Randomized?	Was the Method of Randomization Described and Appropriate?	Was the Treatment Allocation Adequately Concealed?	Blinding of Outcome Assessment?	Was There a Description of Withdrawals and Dropouts?	Total Items Score	Quality Low/High
Andersen, 2000	+	?	−	?	+	2	Low
Badger, 2000	+	+	?	?	+	3	High
Bertelli, 1991	+	?	?	?	+	2	Low
Brambilla, 2006	+	−	−	?	?	1	Low
Carati, 2003	+	+	−	+	+	4	High
Didem, 2005	+	−	−	−	+	2	Low
Dini, 1998	+	?	?	?	+	2	Low
Hornsby, 1995	+	?	−	?	−	1	Low
Irdesel, 2007	+	−	?	−	+	2	Low
Jahr, 2008	+	+	?	?	+	3	High
Johansson, 1998	+	?	?	?	+	2	Low
Kaviani, 2006	+	?	?	?	−	1	Low
Kozanoglu, 2009	+	−	−	?	+	2	Low
Maiya, 2008	+	−	−	−	+	2	Low
McKenzie, 2003	+	−	?	−	+	2	Low
McNeely, 2004	+	+	−	+	+	4	High
Oliveira, 2008	+	−	−	+	+	3	High
Radakovic, 1998	+	?	?	−	?	1	Low
Schmitz, 2009	+	+	+	+	+	5	High
Shaw, 2007	+	?	?	?	+	2	Low
Sitzia, 2002	+	?	?	?	+	2	Low
Szuba, 2002	+	?	?	?	−	1	Low
Tidar, 2009	+	+	+	−	+	4	High
Wilburn, 2006	+	−	?	+	+	3	High
Williams, 2002	+	?	?	−	+	2	Weak

+ indicates met criterion; −, did not meet criterion; ?, unclear.

Table 4. Effect of Interventions on Lymphedema Volume

Intervention	Type of Cancer	Body Region	Total No. of Studies	No. High Quality Studies	No. Studies Finding Significant Benefit	Qualitative: Level of Evidence
Exercise	Breast cancer	Upper extremity	3	2	0	Level 1: strong evidence of neutral impact
Compression bandaging	Multiple cancer types	Upper and lower extremity	1	1	1	Level 2: moderate evidence of benefit for upper and lower extremity; short and long term
Compression garment	Breast cancer Kaposi sarcoma	Upper and lower extremity	3	0	2	Level 2: moderate evidence of benefit for upper and lower extremity
Weight loss intervention	Breast cancer	Upper extremity	1	1	1	Level 2: moderate evidence of benefit in short term
Deep mechanical oscillations with MLD	Breast cancer Melanoma	Breast	1	1	1	Level 2: moderate evidence of benefit in the short term
Flexitouch: mechanically stimulated MLD	Breast cancer	Upper extremity	1	1	0	Level 2: no evidence of benefit
Dietary modification	Breast cancer	Upper extremity	1	0	1	Level 3: limited evidence of benefit in short term
Laser therapy	Breast cancer	Upper extremity	4	1	1	Level 3: limited evidence of benefit in short and long term
Electrically stimulated lymphatic drainage	Breast cancer	Upper extremity	1	0	0	Level 3: no evidence of benefit
Intermittent pneumatic compression	Breast cancer	Upper extremity	4	0	2	Level 3a: conflicting evidence

Table 5. Effect of Interventions on Patient-Rated Outcomes

Intervention	Type of Cancer	Outcomes	Total No. Studies	No. High Quality Studies	No. Studies Finding Significant Benefit	Qualitative: Level of Evidence
Exercise	Breast cancer	Symptoms: pain, tenderness	2	1	1	Level 1: strong evidence of benefit for lymphedema symptoms
		Quality of life	2	1	2	Level 1: strong evidence of benefit for quality of life
Manual lymph drainage	Breast cancer	Symptoms: pain, heaviness, discomfort	3	0	0	Level 2: no evidence of benefit for any symptoms
		Quality of life	1	0	0	Level 3: no evidence of benefit for quality of life
Deep mechanical oscillations with MLD	Breast cancer Melanoma	Symptoms: pain, swelling	1	1	1	Level 2: moderate evidence of benefit for pain and swelling in short term but not at follow-up
Flexitouch: mechanically stimulated MLD	Breast cancer	Quality of life	1	1	0	Level 2: no evidence of benefit for quality of life
Dietary modification	Breast cancer	Symptoms: heaviness, pain, discomfort	1	0	0	Level 3: no evidence of benefit for symptoms
Laser therapy	Breast cancer	Symptoms: pain, heaviness	3	1	1	Level 3: limited evidence of benefit for pain
		Quality of life	1	1	0	Level 3: no evidence of benefit for quality of life

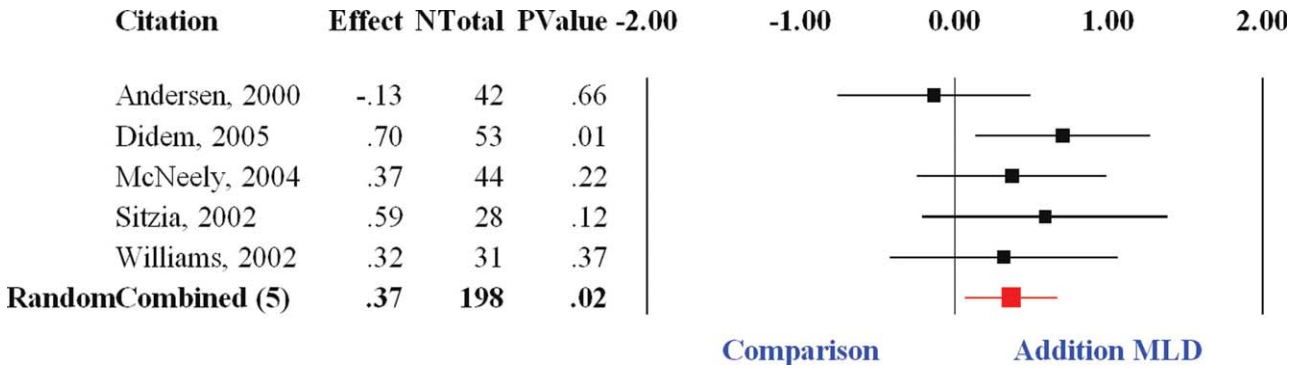

Figure 1. Relative benefit from the addition of MLD in reducing upper extremity lymphedema volume in breast cancer postintervention.

over the 12-week period, and a significant reduction in upper extremity lymphedema volume was observed.

Evidence was found in a single high-quality study[22] supporting the application of a mechanical device called a HIVAMAT that applies deep oscillations (tissue vibration) to the breast to stimulate the flow of lymph in the region. Twenty-two breast cancer/ melanoma participants were randomized to deep oscillations plus MLD or to MLD alone. The treatment consisted of 12 treatments over a 4-week time period. The deep oscillation treatment was found to be effective for reducing breast lymphedema volume and for improving symptoms of pain and swelling after 4 weeks of treatment. No statistically significant differences were found, however, between the groups for outcomes at 12-week follow-up.

Evidence was found in a single high-quality study[36] with 10 participants that examined treatment of upper extremity lymphedema using the Flexitouch device. The Flexitouch is a mechanical device designed to apply a form of mild rhythmic pressure to simulate manual lymph drainage. No statistically significant differences were found for upper extremity lymphedema volume or quality of life between the group receiving treatment with the Flexitouch when compared with the control group performing daily self-massage.

Level 3 Evidence (Limited Evidence)

One study[29] with 10 participants provided evidence of benefit from a combined treatment of DLT and dietary intervention with medium chain triglycerides,[38] compared with DLT alone. In the study, the intervention group received DLT and dietary fats in the form of MCTs, whereas the comparison group received DLT plus a placebo intervention (long chain triglycerides). A significant benefit was found in favor of the combined DLT and MCT intervention for upper extremity lymphedema volume. There was no evidence of benefit, however, for lymphedema symptoms of pain, discomfort, or heaviness.

Four studies[17,24-26] with 128 participants examined the effect of low level laser (LLL) therapy on upper extremity lymphedema volume in breast cancer survivors. Significant benefit was found in favor of LLL treatment in only 1 of the 4 studies.[25] In the study, significant benefit was found for upper extremity lymphedema volume and symptoms of pain for the group receiving LLL treatment combined with daily exercise, compared with the comparison group receiving intermittent pneumatic compression treatment combined with daily exercise. In contrast, in the 1 high-quality study,[17] no significant differences were found between groups receiving LLL treatment and sham LLL treatment. In the remaining 2 LLL studies,[24,26] inadequate data were provided to allow for interpretation of treatment effect.

One study[15] with 74 participants examined the effect of electrically stimulated lymphatic drainage combined with CG versus CG alone. No significant difference was found between the groups for upper extremity lymphedema volume.

Four studies[19,23,30,34] with 170 participants examined the effect of intermittent pneumatic compression treatment on upper extremity lymphedema volume. None of the studies that examined IPC treatments was considered strong. The first study[34] showed benefit from the addition of IPC to DLT treatment in the short term; however, no statistically significant benefit was seen at 40-day follow-up. The second study[30] compared the effect of IPC and CB with a comparison intervention of MLD and CB, finding a statistically significant benefit in favor of

the combined IPC and CB group. In contrast, the third study[23] compared IPC and CG to MLD and CG and found a statistically significant benefit in favor of the group receiving MLD and CG. The fourth study[19] found no significant difference in upper extremity lymphedema volume reduction from treatment with IPC when compared with a no-treatment control.

Level 4 Evidence (No Evidence)

No RCTs were found examining elevation or compression systems; thus, no RCT evidence exists supporting or refuting the benefit of these interventions. Self-massage techniques were a component of treatment for many studies. However, no RCTs have been performed to elucidate the benefit of self-massage treatment alone or as an addition to other treatments. Also, although several studies have examined DLT we were unable to determine its effectiveness, as no studies have compared DLT to standard care (eg, CG) or to a no-intervention control.

Adverse Events

Information on adverse events was provided in 8 studies.[14,17,22,24,28,31,35,36] In 6[17,22,24,31,35,36] of the 8 studies no adverse events occurred. Minor adverse events were reported in 1 study[28] as a result of compression bandaging and included skin reaction (n = 1) and elbow discomfort (n = 1). In another study,[14] 8 participants developed cellulitis during the study period, 1 developed a deep vein thrombosis, and 3 were found to have recurrent cancer.

DISCUSSION

This review summarizes the best available evidence in support of conservative and dietary interventions for lymphedema.

Mixed Cancer Groups

Compression bandaging and compression garments were found to be effective in both short and longterm, and for upper and lower extremity lymphedema secondary to cancer. Studies included patients with breast cancer and Kaposi sarcoma. One study,[14] however, did not report the types of cancer associated with the participants' lymphedema. The findings of our review suggest that the benefits from compression therapy appear to be greater than the estimate of 11% cited in a previous review.[8] Reported percentage reductions achieved through treatment with compression garments or compression bandaging ranged from 17% to 60%. As lymphedema tends to be chronic and lifelong, compression therapies represent simple and relatively low cost options for self-management of the condition.[39]

Breast Cancer

Findings of our meta-analysis demonstrated a statistically significant benefit from the addition of MLD for breast-cancer related lymphedema. In the individual studies, however, only 1 study[18] reported a statistically significant benefit from MLD. The evidence suggests that the effect of MLD in reducing upper extremity lymphedema volume is, on average, potentially smaller than estimated in early, uncontrolled trials. Whereas the analysis shows an additional small benefit from MLD over compression therapy alone, the cost in terms of time and finances to the patient may make provision of this therapy prohibitive. Clinically, it may be reasonable to prescribe compression therapy as a first-line treatment and consider adding MLD if the response to treatment is less than optimal.

The findings of this review support the growing body of evidence from the literature purporting that participation in an exercise program does not exacerbate existing lymphedema in breast cancer survivors. Moreover, exercise was found to reduce the severity of symptoms associated with lymphedema. This is an important finding, as lymphedema and its symptoms may serve as deterrents to participation in regular physical activity and exercise.[31] Research evidence has demonstrated benefit from exercise in improving physical fitness, functioning, and quality of life in breast cancer survivors.[40] Moreover, observational data have shown a protective association between increased physical activity after breast cancer diagnosis and recurrence, cancer-related mortality, and overall mortality.[41] Therefore, the evidence suggests that breast cancer survivors can safely follow a graduated exercise program to achieve health and fitness without fear of worsening existing lymphedema.

Although only 2 studies were found examining nutrition and dietary interventions for lymphedema, positive effects were found in both studies for lymphedema volume reduction. Of note, 1 study[32] demonstrated that caloric reduction for weight loss resulted in a 44% reduction in upper extremity lymphedema volume. Obesity and weight gain are known risk factors for the development of lymphedema, and may be linked to breast cancer recurrence and survival.[42,43] Thus, strategies to promote weight loss/maintenance, such as physical activity and healthy eating, may have additional health benefits beyond lymphedema volume reduction.[38,42]

Strengths and Limitations

The strengths of our review include the use of a meta-analytic approach for examining the effects of MLD on upper extremity lymphedema volume. This approach allowed us to improve power for the primary outcome of upper extremity lymphedema volume, resolve uncertainty for conflicting study findings for MLD, and improve estimates of treatment effectiveness. Although there were some clinical and methodological differences among the included studies, when data were pooled no significant statistical heterogeneity was found. Moreover, the low I-squared value suggests consistency in the evidence among trials despite these differences.

Although the results of our review provide important findings, they must be considered in light of the following potential limitations. Our conclusions regarding the relative effectiveness of conservative interventions are constrained by the wide variability in chosen interventions and comparison treatments, as well as measurement methods. For many interventions, heterogeneity precluded pooling of studies.

Breast cancer continues to be the most extensively studied cancer group for examining conservative interventions for lymphedema. Further research is necessary regarding conservative interventions for lymphedema resulting from other cancers, such as prostate and gynecological cancers. Until the number of studies performed with other cancer populations grows, it is not possible to summarize findings by cancer diagnosis.

The 25 studies included in this review were of variable quality, and only 8 were considered of high quality. Quality criteria designed to assess study bias, such as adequate randomization, concealment of allocation, and blinding of outcome assessors, were commonly not met. Of note, only 1 of the 5 studies examining the addition of MLD was considered of high methodological quality. Our conclusions are tempered by this fact, and further research is needed to confirm our findings.

Conclusions

The evidence suggests that compression garments and compression bandaging are effective in reducing limb lymphedema volume for various types of cancer-related lymphedema. Specific to breast cancer, a statistically significant beneficial effect was found from the addition of manual lymph drainage massage to compression therapy for reducing upper extremity lymphedema volume. Moreover, there is evidence to support exercise and weight loss as strategies to improve lymphedema symptoms and reduce upper extremity lymphedema volume, respectively.

CONFLICT OF INTEREST DISCLOSURES

This review was supported in part through funding from Alberta Health Services Cancer Care. M. McNeely was an investigator in 1 of the primary studies.

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