

BMJ Open Effectiveness of physical exercise programmes in reducing complications associated with secondary lymphoedema to breast cancer: a protocol for an overview of systematic reviews

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ABSTRACT

Introduction Breast cancer-related lymphoedema (BCRL) is one of the most underestimated and debilitating complications associated with the treatment that women with breast cancer receive. Several systematic reviews (SRs) of different physical exercise programmes have been published, presenting disperse and contradictory clinical results. Therefore, there is a need for access to the best available and summarised evidence to capture and evaluate all the physical exercise programmes that focus on reducing BCRL.

Objective To evaluate the effectiveness of different physical exercise programmes in reducing the volume of lymphoedema, pain intensity and improving quality of life.

Method and analysis The protocol of this overview is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, and its methodology is based on Cochrane Handbook for Systematic Reviews of Interventions. Only those SRs involving physical exercise by patients with BCRL will be included, whether on its own or combined with other exercises or other physical therapy interventions. The outcomes of interest to be considered will be lymphoedema volume, quality of life, pain intensity, grip strength, range of motion, upper limb function and any adverse event. The MEDLINE/PubMed, Lilacs, Cochrane Library, PEDro and Embase databases will be searched for reports published from database inception to April 2023.

Two researchers will perform study selection, data extraction and risk of bias assessment independently. Any discrepancy will be resolved by consensus, or ultimately, by a third-party reviewer. We will use Grading of Recommendations Assessment, Development and Evaluation System to assess the overall quality of the body of evidence.

Ethics and dissemination The results of this overview will be published in peer-reviewed scholarly journals and the scientific dissemination will take place in national or international conferences. This study does not require approval from an ethics committee, as it does not directly collect information from patients.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ In order to provide a clear and concise overview, we will use the PRIOR statement.
- ⇒ The study will be carried out according to the recommendation of the Cochrane handbook for overviews of systematic reviews of interventions.
- ⇒ The GROOVE tool will be used to graphically represent the degree of overlap in the primary studies.
- ⇒ The quality of the evidence will be evaluated by using the Grading of Recommendations Assessment, Development and Evaluation System approach.
- ⇒ A potential limitation of this study may be the heterogeneity between published studies that prevents meta-analysing de novo.

INTRODUCTION

According to recent statistics, breast cancer was the most common type of cancer diagnosed in 2020.¹ It has been reported that although breast cancer mortality is diminishing in high-income countries,²⁻⁴ its incidence has been constantly increasing.^{1 5 6} This could be due to substantial improvements in early detection, diagnosis and advances in the treatments being used.^{3 7-12} However, we must also consider that these treatments are not exempt from adverse consequences or effects, including anxiety, alterations in bone health, cardiotoxicity, peripheral neuropathy induced by chemotherapy, alterations in cognitive function, depressive symptoms, falling, fatigue, deterioration in the health-related quality of life, nausea, pain, diminished physical capacity, a decrease of lean mass, an increase of fat mass, altered sexual function, sleep disorders, intolerance of treatment and secondary breast cancer-related lymphoedema (BCRL).¹³

BCRL has been described as one of the most underestimated and debilitating

complications associated with the treatment that women with breast cancer receive.¹⁴ Its reported incidence in the general population varies between 3% and 65%, depending on the type of treatment received and the length of follow-up.^{14–16}

There is currently no clarity on lymphoedema's aetiology,¹⁷ however, it is thought to be caused by an interruption of the lymphatic flow together with other factors,¹⁴ including total mastectomy, axillary dissection positive lymph nodes (>quantity of removed lymph nodes), radiotherapy, use of taxanes and obesity.^{15–35}

Clinically, patients with lymphoedema tend to present swelling in one limb, with an accompanying feeling of weakness.^{36–37} They also refer to a heavy or stiff feeling in the affected limb, restriction of movement in the upper limb, pain or discomfort. In more severe cases, they present a hardening and thickening of the skin (fibrosis).^{36–37} There is greater risk of infection and a chronic, progressive course of the condition, which can lead to cases of anxiety and a deterioration in quality of life.^{38–40}

Physical therapy for BCRL is based on a multimodal therapy approach^{41–42} that includes various interventions such as complete decongestive therapy,⁴³ manual lymphatic drainage,^{44–48} low-level laser therapy,^{49–52} pneumatic pumps,⁵³ kinesio-taping,^{54–56} Yoga,⁵⁷ Pilates⁵⁷ and aquatic therapy,⁵⁸ among other. Many of these interventions are combined during sessions. However, exercise programmes, such as aerobic/endurance training⁵⁹ and resistance training⁵⁹ or a combination of these, are part of physical therapy interventions.⁶⁰

Research reports numerous benefits of different physical exercise programmes in terms of performance, reduction in lymphoedema volume, muscular strength, upper limb function and range of motion, quality of life, pain reduction, cardiovascular function, reduction in body weight and lymphatic circulation,^{57–59–61–73} among others.

Currently, it has been demonstrated that physical exercise has a positive impact on the lymphatic system. This is due to its ability to increase blood flow, cardiac output and blood pressure, thereby promoting capillary filtration and entry of fluids and proteins into lymphatic capillaries.^{74–76} Furthermore, exercise increases lymph propulsion through lymphatic vessels through intrinsic and extrinsic mechanisms, such as skeletal muscle pumping, respiratory pumping and pulse of nearby blood vessels, facilitating lymph return.^{74–76}

Currently, there is a large quantity of systematic reviews (SRs) that evaluates the different physical exercise programmes for the reduction of BCRL. However, different SRs that combine this information have been published, presenting disperse and contradictory clinical results.^{57–59–61–63–65–67–69–70–72–77–92}

There are currently no studies that summarise and evaluate the effectiveness of all the SRs that include randomised clinical trials (RCTs) on the different physical exercise programmes focused on the reduction of BCRL.

Overviews of SRs compile information from multiple SRs to provide a comprehensive synthesis of evidence, providing a wider perspective on the heterogeneity, possible sources of bias and methodological quality of SRs that may affect the certainty of evidence. Overviews are designed to be accessible and easy-to-use documents, and tend to present a much broader reach than any single SR.^{93–95}

There is a need for access to the best available and summarised evidence to capture and evaluate all the physical exercise programmes that focus on reducing the volume of lymphoedema and complications associated such as poor quality of life, pain intensity, grip strength, range of motion, upper limb function and any adverse events in patients with BCRL.

Therefore, the results that can be obtained by this overview will provide relevant information for clinical decision making for patients, researchers, physical therapists, physicians and stakeholders.

Research question

Are different physical exercise programmes effective and safe in patients diagnosed with BCRL?

Objective

To evaluate the effectiveness of different physical exercise programmes in reducing the volume of lymphoedema and pain intensity and improving quality of life. Secondly adverse events, grip strength, range of movement and upper limb function will be also evaluated.

METHODS AND ANALYSIS

This research protocol has been reported following the reference items for publishing SRs and Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols⁹⁶ (online supplemental appendix A). This overview is registered in the PROSPERO database (CRD42022334433). Any amendments to the protocol will be made through PROSPERO.

We will use a focus that allows us to summarise the evidence from more than one SR of different interventions (all physical exercise programmes) for the same condition or problem (BCRL).⁹⁷

When reporting the overview, we will use the Preferred Reporting items for Overviews of Reviews (PRIOR) statement⁹⁸ and the methodology will be conducted based on the Cochrane Handbook for Systematic Reviews of Interventions.⁹⁷

Patient and public involvement

None.

Eligibility criteria for study type

SRs with or without meta-analysis will be included.⁹⁵ They must present an explicit methodology that corresponds to an SR⁹⁹; clearly articulated objectives and questions to be addressed, inclusion and exclusion criteria stipulated a priori that determine the eligibility of studies, use a

search strategy in two or more databases (eg, MEDLINE, Lilacs), appraisal of the quality of included studies,¹⁰⁰ and the included primary studies should correspond to RCTs. In addition, SRs that were conducted using a rapid review methodology will be included.¹⁰¹ If SRs include studies with other primary study designs, they will only be included if the data from the RCTs are reported in a disaggregated manner, allowing for extraction of their information. SRs protocols, scoping review and narrative reviews will be excluded. We will only include studies that are written in English, Spanish or Portuguese.

Eligibility criteria for participants and context

We will include SR where the patients have a diagnosis of BCRL.

Eligibility criteria for the intervention

We will include SRs that incorporate any type of physical exercise programme (eg, resistance training, aerobic exercise, yoga, Pilates), either on its own or in combination with other exercises or other physical therapy interventions (eg, complete decongestive therapy, manual lymphatic drainage, low-level laser therapy).

Eligibility criteria for the comparison

We will include SRs where the comparison group is the usual care without exercise, without treatment or education, or any other type of physical therapy.

Eligibility criteria for the outcomes

The following primary outcomes will be considered:

- ▶ Volumetric changes in arm. The volume could be measured in any of the following ways, all of which made a comparison with the unaffected side (lymphoedema volume,^{102 103} volume reduction,^{102 104 105}; per cent reduction^{102 104–106}), which must be measured by any of the following valid methods: water displacement volumetry, measurement of the limb's circumference, bioimpedance spectroscopy, dual X-ray absorptiometry and perometry (online supplemental appendix B).
- ▶ Quality of life, which must be evaluated by any validated generic or specific self-report scale (eg, EORTC-QLQ-C30).
- ▶ Pain intensity, which must be evaluated by validated generic or specific self-report scale (eg, Numerical Rating Scale or Visual Analogue Scale).

The following secondary outcomes will be considered:

- ▶ Adverse events from the physical exercise programmes such as an increase in lymphoedema volume and pain.
- ▶ Grip strength in patients undergoing physical therapy interventions, evaluated with dynamometry.
- ▶ Range of motion in patients undergoing physical therapy interventions, evaluated with goniometry.
- ▶ Upper limb function, which must be evaluated by any validated generic or specific self-report scale (eg, Disabilities of the Arm, Shoulder and Hand (DASH)).

Search strategy

We will perform a search of SRs of RCTs in the following electronic databases: MEDLINE/PubMed, Embase, Cochrane Library, PEDro and Lilacs will be searched for reports published from data base inception to April 2023.

The search strategy will present a highly sensitive focus and the use of controlled language (MeSH, Emtree or DeCS) and natural language.¹⁰⁷ The details of the search strategy used in the databases are described in online supplemental appendix C.

Selection process

The records provided from the different databases will be exported to the Rayyan platform (<https://www.rayyan.ai/about.html>).¹⁰⁸ After eliminating duplicated articles, two researchers will independently select the studies by reading the titles and abstracts. Then, the same researchers will independently review the full texts of the potentially eligible records. Any discrepancy will be resolved by consensus, or ultimately by a third-party reviewer. A table will descriptively explain which studies are excluded once the full text has been read.

Managing overlapping SRs

We recognise that the SRs to be included in this overview will address very similar research questions. Therefore, it is probable that they will include several of the same primary studies. If we find overlapping SRs, we will avoid double counting data by ensuring that the findings of each primary study are separately extracted one time only.⁹⁵

To evaluate the overlapping of primary studies included in the SRs, we will create a matrix to visually present the amount of overlapping.¹⁰⁹ Then, we will evaluate the degree of overlapping in the primary studies by using the 'corrected covered area' (CCA), as it represents the proportion of repeated occurrence of primary studies in other SRs, divided by the number of unique primary studies. The degree of overlapping of primary studies between SRs will be interpreted and reported as follows: slight (0%–5%), moderate (6%–10%), high (11%–15%) and very high (>15%).¹⁰⁹ The CCA will be calculated and plotted by means of Graphical Representation of Overlap for OVERviews tool (GROOVE tool).¹¹⁰

Data extraction

Two researchers will independently compile the information of the data extracted from each one of the included SRs, using a standard Excel worksheet. A third author will check extracted information and will solve discrepancies.

The data to be extracted will consider:

- ▶ Details of the SRs publication: authors, year published, research team, associated institutions, involved countries, databases included in the SRs and type of synthesis (qualitative or quantitative).
- ▶ Type of participants: number and characteristics.

- ▶ Characteristics of the intervention: modality of physical exercise programme, if is a multicomponent exercise programme or a sole intervention, intensity, dosification and duration of the programme.
- ▶ Type of comparisons.
- ▶ Reported outcomes.
- ▶ Derived conclusions.

Assessment of the methodological quality of the included reviews

Two researchers will be responsible for the methodological assessment. Any discrepancy will be resolved by consensus, or ultimately by a third-party reviewer.

According to the Cochrane handbook's requirements, both the methodological quality of the included reviews and the quality of evidence from the individual studies included in the reviews must be assessed.

The methodological quality of the included SRs will be assessed using the ROBIS (Risk of Bias in Systematic Review) tool.¹¹¹ This tool has been developed using a rigorous methodology and is focused on four epidemiological categories of SRs: intervention, diagnosis, prognosis and aetiology.¹¹¹

The ROBIS tool has been made for authors that summarise SRs, and that require evaluating the risk of bias in their reviews.¹¹¹

The ROBIS tool is completed in three phases¹¹¹: (1) assess relevance (optional); (2) identify concerns with the review process (study eligibility criteria, identification and selection of studies, data collection and study appraisal, synthesis and findings); (3) judge risk of bias (Concerns with the review process (phase 2), three questions related to the interpretation of the review's findings are answered and global assessment). Answers to the signal questions are categorised as 'yes', 'probably yes', 'no', 'probably no' or 'no information'. The risk of bias is judged as 'high', 'low' or 'unclear'.

Quality of evidence in the primary studies included in reviews

If the SRs included in our overview report the risk of bias through the second version of Cochrane collaboration methodological tool (RoB 2),¹¹² we will extract this information and it will be used in our evaluation. Meanwhile, if the SRs do not use RoB 2, we will assess the risk of bias of the individual trials included in the SRs using the RoB 2, which include the following domains: bias derived from the randomisation process, bias due to deviations from planned interventions, bias due to lack of results data, bias in the measurement of the result, and bias in the selection of the reported result.

A series of signalling questions that aim to provide a structured approach to obtaining relevant information on bias risk assessment will be included for each domain. For each domain, the possible risk of bias judgements will be reported as: low risk of bias, some concerns and high risk of bias.⁵⁹

The Grading of Recommendations Assessment, Development and Evaluation System (GRADE) will be used to evaluate the overall quality of evidence related to the estimated effects of the different physical exercise programmes, whether on their own or combined with other exercise or physical therapy interventions on the reduction of secondary lymphoedema associated with breast cancer, quality of life, decrease of pain, articular range, grip strength.^{113 114} Therefore, if the included SRs report the certainty of evidence through the GRADE methodology, the information will be extracted and used in our overview. But, if the included SRs do not present or evaluate the quality of evidence with the GRADE methodology, we will evaluate and report the certainty of evidence using the GRADE methodology. The criteria evaluated by GRADE are: 'study design', 'risk of bias', 'inconsistency', 'indirectness', 'imprecision', 'suspected publication bias', 'other considerations'.^{115 116}

GRADEproGDT software (www.grade-pro.org) will be used to generate the 'findings of summary' tables, which will indicate the principal results with their respective quality of evidence evaluation.

We will use four levels of evidence, according to the GRADE working group's recommendations¹¹⁷:

- ▶ High quality: it is very unlikely that additional studies change our confidence in the estimated effect.
- ▶ Moderate quality: it is likely that additional research has an impact on our confidence in the estimated effect and may change the estimation.
- ▶ Low quality: it is very likely that additional research has an important impact on our confidence in the estimated effect and will probably change the estimation.
- ▶ Very low quality: little confidence in the estimated effect.

Data synthesis

The results will be reported according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions. We will also use the PRISMA flow chart to indicate the study selection process.

We will summarise the scientific evidence presented on the different exercise programmes and the reduction of secondary lymphoedema associated with breast cancer.

The characteristics of the included SRs (details of the SRs publication; type of participants: number and characteristics; characteristics of the intervention; type of comparisons; reported outcome of interest; derived conclusions), will be reported in tables that summarise all relevant information.

When overlapping SRs are found, we will avoid double counting data. We will ensure that the findings of each primary study are separately extracted one time only. However, assuming that there will be overlapping RCTs in different SRs, we will reanalyse the results, which will mean extracting and reanalysing all information corresponding to primary studies in the included SRs. In order to avoid the inclusion

of indirect evidence, we will verify whether or not the RCTs included in the SRs answer our overview's research question.

Therefore, we propose carrying our new meta-analyses for each comparison and outcome of interest, considering subgroups by exercise modality or programme. We will use relative risk as a measure of effect for the dichotomous outcome data, with its respective 95% CI. When the outcome of interest is measured on the same scales, we will present the continuous interest outcomes as mean differences (MD), with their respective 95% CI. The standardised MDs will be calculated when the outcome of interest are measures on different scales.

Heterogeneity will be evaluated using the inconsistency test (I^2). We will use the following heterogeneity classification values: (1) 0%–40% might not be important; (2) 30%–60%: may represent moderate heterogeneity; (3) 50%–90% may represent substantial heterogeneity and (4) 75%–100% considerable heterogeneity.¹¹⁸ The data will not be pooled if I^2 was over 75%. If meta-analysis is not plausible or appropriate, the comparable RCT outcomes will be qualitatively described in the text. If a statistical heterogeneity of >75% is presented, other sources of heterogeneity will be explored. The reporting biases will be evaluated if at least 10 RCTs are included in the meta-analyses. We will use the Begg's test to analyse the funnel plot.^{119 120} If there are asymmetries, we will examine other causes in addition to reporting bias, such as selective outcome reporting, poor methodological quality in smaller studies and heterogeneity. We will perform a sensitivity analysis only if we are able to find an appropriate number of studies. This analysis will include the following:

- Restricting the analysis to studies that present a low risk of bias.

Ethics and dissemination

This overview's results will be published in peer-reviewed academic journals and the scientific dissemination will take place in national or international conferences relevant in this area of study and/or specialty.

This study does not require approval from an ethics committee, as it does not directly collect information from patients.

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