

Ultrasound therapy and transcutaneous electrical neuromuscular stimulation for management of post-mastectomy upper limb lymphedema

Terapia de ultrassom e estimulação elétrica transcutânea neuromuscular para a tratamento do linfedema de membro superior pós-mastectomia

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ABSTRACT

Objective: This article aims to assess the effect of transcutaneous electrical stimulation or ultrasound therapy in the treatment of post-mastectomy upper limb lymphedema. **Method:** A systematic literature review was performed from 1980 to 2012 from the MedLine, Cochrane Library, LILACS and SciELO databases. The terms used in the search were (breast neoplasm OR breast cancer OR lymphedema) and (hyperthermia, induced OR diathermy OR ultrasonic therapy OR ultrasound OR transcutaneous electrical nerve stimulation OR TENS). The selections of the studies concerned female patients with post-mastectomy upper limb lymphedema who underwent diathermy by ultrasound therapy and transcutaneous electric nerve stimulation. Only randomized (RCT) and quasi-randomized study designs were included (both Narrow and Broad Therapy). Only studies published in the full paper format were included. After reviewing the 2,158 abstracts resulting from the search, only two papers were selected. Two researchers analyzed the two articles, using the Van Tulder and JADAD scales for quality assessment. **Results:** Both papers evaluated the use of ultrasound therapy and electric stimulation for treatment of post-mastectomy lymphedema. A total of 132 subjects were included in these two studies, and little improvement was observed in pain reduction or quality of life. Only the study using ultrasound therapy identified a small reduction in lymphedema symptoms; however, evidence supporting the application of this method is lacking. **Conclusion:** Further studies are needed to evaluate the use of ultrasound therapy or electrotherapy for treatment of post-mastectomy lymphedema and to evaluate the potential effect of these therapies on later development of metastatic disease.

Keywords: Breast Neoplasms Lymphedema, Rehabilitation, Transcutaneous Electrical Nerve Stimulation

RESUMO

Objetivo: Avaliar o efeito da estimulação elétrica transcutânea ou terapia de ultra-som no tratamento de pós-mastectomia linfedema do membro superior. **Método:** revisão sistemática da literatura foi realizada 1980-2012 do MedLine, Cochrane Library, LILACS e SciELO. Os termos utilizados na pesquisa foram (neoplasia de mama ou câncer de mama ou de linfedema) e (hipertermia, induzido ou diatermia ou terapia de ultra-som ou ultra-som ou a estimulação elétrica nervosa transcutânea ou dezenas). As seleções dos estudos eram de pacientes mulheres com linfedema pós-mastectomia membro superior que foram submetidos a diatermia por terapia de ultra-som e estimulação elétrica nervosa transcutânea. Só randomizado (RCT) e projetos quase randomizados do estudo foram incluídos (ambos estreita e Broad Therapy). Somente estudos publicados no formato de artigo completo foram incluídos. Depois de analisar os 2.158 resumos resultantes da pesquisa, foram selecionados apenas dois artigos. Dois pesquisadores analisaram os dois artigos, usando o Van Tulder e JADAD escalas para avaliação da qualidade. **Resultados:** Ambos os trabalhos avaliaram o uso da terapia de ultra-som e estimulação elétrica para o tratamento do linfedema pós-mastectomia. Um total de 132 indivíduos foram incluídos em ambos os estudos, e pouca melhora foi observada em redução ou a qualidade de vida da dor. Somente o estudo usando a terapia de ultra-som identificada uma pequena redução nos sintomas de linfedema. No entanto evidências que suportam a aplicação deste método está faltando. **Conclusão:** Mais estudos são necessários para avaliar o uso da terapia de ultra-som ou eletroterapia para o tratamento de linfedema pós-mastectomia e para avaliar o efeito potencial dessas terapias no desenvolvimento posterior da doença metastática.

Palavras-chave: Neoplasias da Mama, Linfedema, Reabilitação, Estimulação Elétrica Nervosa Transcutânea

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INTRODUCTION

Almost 1.4 million women worldwide were diagnosed with breast cancer in 2008 and approximately 459,000 deaths were registered. The estimated 5-year survival rate varies from almost 90% in the United States of America, Australia, and Canada, to 12% in certain regions of Africa. This difference is related to a combination of early detection, access to treatment, and cultural barriers. Approximately 230,000 new invasive breast cancer cases were likely diagnosed in 2012, and almost 40,000 patients aged between 40 and 59 years will die as a result of this disease.¹

Lymphedema is one complication that can result from disruption of post-breast cancer ganglion drainage. It is a poorly understood, relatively underestimated, and little studied disease entity. Reported incidence rates for secondary lymphedema vary depending on the method used for measurement. Inconsistent definitions and the lack of a standard classification system have resulted in diverse incidence rates for secondary lymphedema, ranging from 2.4% to 56% within 2 years after surgery.² Most women (71%) develop secondary lymphedema within 12 months after surgery for breast cancer, although the condition may occur within a few days and up to 30 years after initiation of treatment.³

Lymphedema can result in significant physical and psychological morbidity. Swelling causes a disproportionate increase in the size of the body part and thus can interfere with mobility and affect the patients' body image.⁴ In addition to an increase in size, the affected subcutaneous tissues gradually thicken and become fibrotic, creating a solid component of swelling.⁵ Pain and discomfort are among the physical problems associated with lymphedema, in addition to recurrent attacks of infection/inflammation. The latter are a result of reduced local immunity in the affected part of the body. The limb shape can become distorted.⁶ Post-breast cancer lymphedema may also significantly influence function and quality of life.⁷

There is no cure for lymphedema, and after its occurrence, regression is difficult to achieve. The main goals of treatment are controlling volume increases in the affected limb, alleviating symptoms, and generally preventing complications related to lymphedema.⁸ Because drugs are not very beneficial for the treatment of lymphedema, rehabilitation programs that combine massage, skin care, exercises, and compressive methods are the treatments of choice.⁹ Complex decongestive

physical therapy (CDPT), the most well-studied treatment, is a combined program that incorporates manual lymph drainage, multi-layer short-stretch bandaging, exercise, and skin care. CDPT has been recommended by a consensus panel of experts and is considered to be the standard approach to lymphedema management.¹⁰ Several elements of CDPT have proven efficacy, with reports of an approximately 50% initial reduction in the measured excess limb volume. Other therapeutic options include intermittent pneumatic compression therapy (IPC), Manual Lymphatic Drainage (MLD), constraint therapies with elastic bandages, kinesiotherapy, surgery, and more recently, laser treatment.¹⁰⁻¹²

According to the literature, the therapeutic benefits of transcutaneous electrical neuromuscular stimulation (TENS) or ultrasound therapy (US) remain controversial, in spite of the biophysical effects of these therapies.¹³⁻¹⁷ The justification for using US to treat lymphedema is the "soft action" exerted through wave propagation at the cellular level, with a slight heat (joule effect) that modifies cell metabolism and microcirculation. It is thought that these processes may promote lymph flow and possibly reduce the firmness and fibrosis commonly observed after CDPT. The proposed mechanism of electrotherapy is similar to that of manual lymphatic drainage. Both therapies return lymph to lymphatic circulation, though electrotherapy may have an additional molecular protein activation effect.

Jahr et al.¹⁸ used intermittent, low intensity, extremely low frequency electrostatic fields to stimulate lymphatic flow by deep resonance vibration. They reported alleviation of pain and reduction of swelling in patients with breast lymphedema related to breast cancer. Ricci¹⁹ evaluated the effects of an electro-medical instrument that uses low-frequency and low-intensity electrotherapy to treat lymphedema by activating the biological structures contained in the lymph through the physical process of bioresonance. He applied this therapy to 50 patients and used lymphoscintigraphy to verify the effects. The study concluded that the treatment stimulates lymph flow, activates apical limb lymph nodes and reduces dermal back flow. They reported that the low-frequency low-intensity electrotherapy system was useful in diminishing the volume and the 'feeling of gravity and hardening'. While the study by Ricci¹⁹ provided the first published data on the effect of electric fields for the treatment of upper and lower limb lymphedema, there was no information reported regarding the magnitude of the effects.

Zhang et al.²⁰ studied 1,045 patients with chronic lymphedema and demonstrated a volume reduction after heat and bandage treatment.

Despite these promising results, studies using modalities that generate heat or electricity in cancer patients have been conducted with caution. The published results are promising and the method is simple. However, American experts in physical medicine and rehabilitation have long advised that any modality that generates electricity or heat (e.g., shortwave diathermy, microwave diathermy) should be used with caution in people with active cancer, due to the possibility of increasing tumor growth and metastasis. A well-controlled, randomized trial involving mice receiving subcutaneous injections of tumor cells demonstrated that therapeutic ultrasound led to increases in tumor growth, although it did not increase the occurrence of metastasis.²¹ Because it is often unknown whether breast cancer is truly in remission, the possibility of recurrence (i.e., active cancer) should always be considered.

In spite of the above considerations, US and electrotherapy are common and longtime key modalities used in rehabilitation. Moreover, the possibility of maximizing positive outcomes in breast cancer patients without side effects through the use of appropriate rehabilitation approaches provides an important opportunity for involving the rehabilitation team in the care of cancer patients.

Based on this notion, the present systematic review evaluates the effects of using transcutaneous electrical stimulation and/or ultrasound in the treatment of post-mastectomy upper-limb lymphedema. This study focuses on US and electrotherapy treatment in the context of clinical benefits and lymphedema reduction as well as studies investigating possible side effects such as increased tumor growth or metastasis.

OBJECTIVE

The objective of this study was to assess the effects of transcutaneous electrical stimulation and ultrasound therapy in the treatment of post-mastectomy upper limb lymphedema.

METHOD

This paper is the result of a systematic literature review, from the period between 1980 and 2012, which was performed using the MedLine, Cochrane Library, LILACS, IBECs, and SciELO databases. The MeSh terms were

identified, and the PICO search strategy methodology was used, where P = patient, I = intervention, C = comparison among therapies, and O = outcome. The search was performed with the use of the following terms: (breast neoplasm OR breast cancer OR lymphedema) and (hyperthermia, induced OR diathermy OR ultrasonic therapy OR ultrasound OR transcutaneous electric nerve stimulation OR TENS).

The following articles were found by the search outlined above: Case Reports (1,497); Clinical Prediction Guides/Broad (2,042); Clinical Trial (561); Diagnosis/Broad (6,195); Etiology/Broad (3,131); Humans (8,206); Meta-analysis (19); Multicenter Study (145); Prognosis/Broad (2,309); Review (1,169); Therapy/Broad (1,999); and Therapy/Narrow (159).

Inclusion and exclusion criteria

- Type of population: female patients who presented with post-mastectomy upper limb lymphedema.
- Types of studies: according to the objective of this study, i.e., treatment analysis, only clinical trials were assessed (both Narrow and Broad Therapy). Randomized (RCT) and quasi-randomized study designs were included. Quasi-randomized studies were defined as those that do not strictly adhere to randomized methods of allocation, i.e., allocation by order of admission, date of birth, or some other method that is not truly random. Only full paper publications were deemed acceptable for review.
- Types of interventions: induced or diathermy by ultrasound therapy and transcutaneous electrical nerve stimulation.
- Types of outcome measures: at least one key symptom of lymphedema, including subjective circulation, pain, physical function, and/or decreased fibrosis. Secondary outcome measures included adverse events such as the risk of inducing metastasis - including bone metastasis - in active cancer patients, or the potential for relapse in areas such as the ribs, thoracic wall, or axillae. The hematogenous dissemination of these metastases was thought to be due to the thermal effect of ultrasound therapy through promotion of heat production and enlargement of the blood vessels or through increasing the nutritional blood flow to the tissues, which also favors tissue regeneration.

After completing the search and reading the narrow therapy abstracts, 157 of 159 were excluded, as they did not focus on the treatment of post-mastectomy lymphedema, but instead on diagnosing or treating lymphedema due to other causes. Only 2 of the articles, according to the abstracts, were pertinent to our research question. After evaluation of the complete articles, we excluded one of them because the treatment of lower-limb lymphedema was not within the scope of the present study. Approximately 1,999 broad therapy articles were found. After evaluating the abstracts, 1,993 were excluded and 7 complete articles were evaluated. Five of those were excluded for not using US or TENS. One study was excluded because the lymphedema was not assessed using volumetric or circumferential measurement.

The analyses of the two selected articles were performed by two researchers using the Van Tulder and JADAD scales for quality assessment.

The Van Tulder criteria score trials according to 19 items: 11 items assess internal validity, 6 items assess descriptive quality, and 2 items assess statistical validity. The maximum Van Tulder score is 18 points. Trials are considered to be of high methodological quality if their internal validity is $\geq 5/10$. To take a more comprehensive look at the methodological quality, the trials in this review were categorized according to the following criteria:

- High quality trials: At least 70% of the methodological criteria met an internal validity of $\geq 6/10$;
- Medium quality trials: At least 50% of methodological criteria met internal validity of $5/10$;
- Low quality trials. At least 50% of methodological criteria met plus internal validity $< 5/10$.

RESULTS

According to the methodology described above, two articles were included, one using narrow therapy and the other broad therapy (Chart 1).

It was noted that one of the articles was considered to be of low quality, with a Van Tulder score of 3 and JADAD score of 1.

The results were 9,607 records identified, 12 records after duplicates were removed, 2,158 records screened, and 2,149 records excluded. Nine full text articles were assessed for eligibility and 7 were excluded because they did not use either US or TENS. Qualitative synthesis was 2 articles.

Study characteristics Participants and Interventions

A total of 132 subjects were included from the two studies; 36 from Belmonte et al.²² and 96 from Balzarini et al.²³

Belmonte et al.²² randomized 36 patients into two intervention groups (A and B); the objective was to compare the efficacy of low-frequency, low-intensity electrotherapy vs. manual lymphatic drainage for the treatment of chronic upper limb breast cancer-related lymphedema. The design was a crossover single-blind randomized clinical trial in a rehabilitation setting. Thirty-six women with chronic upper limb breast cancer-related lymphedema were enrolled.

Patients were recruited by the physician in an outpatient hospital rehabilitation setting between March 2008 and July 2009. Inclusion criteria were the presence of breast cancer-related lymphedema, completion of the intensive phase of complex decongestive therapy for lymphedema, initiation of the maintenance phase at least 1 year prior to the study, and a documented therapeutic clearance period with no manual lymphatic drainage treatment for at least 6 months. Exclusion criteria were the following: (1) the presence of a pacemaker, heart disease, pregnancy, metallic devices in the affected limb, infectious disease, epilepsy, thrombophlebitis, arterial hypertension and metastasis, and (2) the presence of mental, sensory, or language problems which could hinder participation. At recruitment, patients had a mean age of 67.8 years, and their average body mass index was 30.5 kg/m². All patients had been surgically treated, 56% by breast-conserving surgery. All patients had undergone axillary node dissection, while only four had previously undergone a sentinel lymph node biopsy. Almost all patients (87.5%) used compression garments (four patients did not use garments because of skin problems or personal choice), and 46.9% had a history of cutaneous infectious complications.

Patients were randomized to undergo either low-frequency low-intensity electrotherapy followed by manual lymphatic drainage (group A with 19 patients), or 10 sessions of manual lymphatic drainage followed by 10 sessions of low-frequency low-intensity electrotherapy (group B with 17 patients). There was a month of washout time between treatments.

Physicians who examined the patients and performed the data analysis were blinded to the treatment received. To ensure that blinding was successful, patients were advised not to mention their treatment during physician evaluation, except for adverse effects. There

Chart 1. Description of the articles included

Year	Author	Country	Intervention	Outcome	Result
2011	Belmonte et al. ²²	Spain	Low frequency TENS and Manual Lymphatic Drainage	Comparing the effectiveness of TENS and MLD in the reduction of post-mastectomy lymphedema	No significant differences were observed between manual lymphatic drainage and low-frequency TENS, there was reduction of lymphedema, alleviation of pain, sensation of weight, constraint, and improvement in quality of life.
1993	Balzarini et al. ²³	Italy	Ultrasound Therapy (UST) and elastic compression, UST with no other physical means; Mechanical Compressive Therapy (MCT) and elastic compression and MCT with no other physical means.	Comparing the effectiveness of UST applied to the acupuncture points of the upper limb: ST (stomach), LU (lung), LI (lower intestine), SI (smaller intestine), SJ (San Jiao), and HT (heart), with the MCT either associated or not with elastic	In the ultrasound group, the average arm size was reduced by about 8.78% and in the mechanical compression about 9.13%. No additional improvement was observed combining the use of elastic compression with UST or MCT.

were no reported adverse effects resulting from the manual lymphatic drainage treatment. It was verified that one patient suffered an episode of erysipelas on the fourth day of treatment with low frequency and intensity electrotherapy. This patient refused to go to a hospital for evaluation until 3 weeks later, at which point the erysipelas had disappeared. Another patient presented with erythema on the back of her hand on the third day of electrotherapy, which was attributed to a crease in her clothes. When the clothing item was removed, after 2 days, the erythema abated and she continued with the treatment sessions. A third patient presented with irritation on her skin at the spot where the electrode was attached for electrotherapy. When the intensity was reduced, her symptoms abated and she was able to complete all treatment sessions. A physiotherapist with expertise in lymphedema treatment performed both treatments. During both treatment periods, the maintenance phase of complex decongestive therapy was continued: compression therapy using adapted garments (sleeves and gloves) was utilized, and patients were reminded to continue exercises and skin care.

In the study by Balzarini et al.,²³ 96 patients were randomized into four groups as follows: 35 patients used mechanical pressure therapy (MPT) and elastic sleeves; 30 patients used only mechanical pressure therapy; 15 patients used ultrasound therapy and elastic sleeves; and 16 patients used only ultrasound therapy. In both US groups, the US was performed on the lymphedema-affected upper limb using acupuncture points of the following local meridians: ST (stomach), LU (lungs), LI (lower intestine), SI (small intestine), SJ (san jiao), and HT (heart), according to the swollen areas, with a total of 10 sessions. Ultrasound was applied in 3 cycles using the following parameters: 30-minute duration per day for 10 consecutive days, using 2 watt/cm² power at a frequency of 3 MHz for 5-second cycles. The MPT parameters were 6 hours per day for 5

consecutive days at a pressure of 40 mmHg for 1 year with a 4-month interval for follow up and lymphedema measurement of the affected limb using the contralateral limb as a control. Twelve patients reportedly left the study, 5 in the US group due to cancer recurrence, and 7 in MPT group for not adhering to the treatment protocol. In both US groups, 11 patients had undergone radical mastectomy without radiotherapy, and 20 were submitted to quadrantectomy with axillary dissection and radiotherapy. In both MPT groups, 19 patients had undergone radical mastectomy and 46 conservative operations were performed. The interval between surgical intervention and the onset of arm edema ranged from 3 to 52 months in the US groups, and from 5 to 57 months in the MPT groups.

Effects of interventions Lymphedema

In both studies, the lymphedema was evaluated measuring circumference to assess the reduction in edema. In one of the studies, this method was also used for comparison with the contralateral limb.²³

In the study by Belmonte et al.,²² there were no differences between the groups. When comparing the effects of low-frequency low-intensity electrotherapy with manual lymphatic drainage, there were no significant differences in lymphedema, except for a marginally significant reduction of pain that was greater in group A (13.1 vs. 1.07 mm) ($p = 0.05$). Analysis before and after low-frequency low-intensity electrotherapy treatment data showed a non-significant lymphedema volume reduction of 19.77 mL ($p = 0.36$). Although statistically significant benefits were observed in the low-frequency low-intensity electrotherapy group with regards to most symptoms and the health-related quality of life, the observed benefits were not significantly different from those observed in the manual lymphatic drainage group. The edema was reduced by practically the same

proportion in both groups²² with no great differences in limb size pre- and post-treatment.

The Balzarini et al.²³ study reported a greater reduction in volume after the first 4 months of treatment in the US group; however, this effect did not persist at 12 months. At baseline, the mean arm size-difference was 8.78% in the US groups and 9.13% in the MPT groups, which is not a significant difference. After 12 months, the size difference was 6.88% in the US groups and 7.55% in the MPT groups, which is also not a significant difference.

US was as effective as MCT with regards to edema reduction, but was better tolerated than MCT.²³ It was noted that the use of an elastic sleeve did not produce any additional improvement in the percentage of volume reduction.

Pain

Pain was assessed in the Belmonte et al.²² study using the VAS score. Pain, heaviness, and tightness were significantly reduced after electrotherapy; however, no significant differences were observed when compared to manual lymphatic drainage. Nonetheless, there was no statistically significant difference between low-frequency low-intensity electrotherapy and manual lymphatic drainage for these symptoms.

Fibrosis

Tissue fibrosis was evaluated in the study by Balzarini et al.,²³ who found a reduction in fibrosis with a greater degree of subjectively perceived tissue softening in the ultrasound-treated group.

DISCUSSION

This paper is a systematic literature review spanning the period between 1980 and 2012 that aimed to assess the effects of transcutaneous electrical stimulation and ultrasound therapy in the treatment of post-mastectomy upper limb lymphedema. Our search and

methodological strategy resulted in just two randomized clinical studies focused on the treatment of post-breast cancer surgery lymphedema with US or TENS: one of high quality and one of low quality. Neither of the studies referred to the margin of safety related to the region of application of US or TENS, due to active areas or areas with a high potential for breast cancer metastasis, including bone metastasis to the ribs, thoracic wall, or axillae.^{24,25}

Belmonte et al.²² is the first study to compare low-frequency low-intensity electrotherapy to manual lymphatic drainage for several relevant outcomes (limb volume, pain, heaviness, tightness, and health-related quality of life) in patients with chronic breast cancer-related lymphedema. Although the benefits of electrotherapy on most symptoms and the health-related quality of life were significant, they were not significantly different from those observed with manual lymphatic drainage. In fact, any improvement in health-related quality of life was merely observed.²² In terms of lymphedema volume change, the effect of low-frequency low-intensity electrotherapy was negligible, as was the effect of manual lymphatic drainage. This was likely because treatment was utilized in a sample of previously treated patients with well-controlled lymphedema who were in the maintenance phase of treatment. This aspect may have limited the potential degree of the benefit, as the patients' disease was well controlled with previous periodic treatment sessions (once or twice per year) with manual lymphatic drainage. Moreover, most patients (87.5%) regularly used compression garments, which is an important factor in stabilizing lymphedema volume in the maintenance phase. However, the treatment was well-tolerated, and there were no significant adverse effects observed. This trial also had significant limitations. The small sample size and the fact that patients were not blinded to the treatment they received presented the greatest potential for bias. Additionally, including only chronic lymphedema patients limits the conclusion to only the chronic phase. The effect of electrotherapy in early lymphedema and in the intensive phase of lymphedema treatment would require future studies. In addition, the study was designed to determine the immediate effect after 10 sessions of treatment with no further follow-up. Lastly, both treatments showed additional benefits when administered in sequence. This could indicate that combined treatments may result in greater therapeutic benefits than electrotherapy alone. Taking these observations into account, more studies are needed

to assess the effects of electrotherapy in the management of lymphedema patients in all phases of treatment.

The study by Balzarini et al.,²³ which examined the use of Ultrasound Therapy (US) and Mechanical Pressure Therapy (MPT), isolated or associated with elastic compression, did not show a great difference in the reduction of edema. However, the US treatment was better tolerated than MCT.²³ Additionally, although there was a similar degree of volume reduction in both groups, there was a greater degree of subjectively perceived tissue softening in the ultrasound-treated group. More studies are warranted to assess whether US therapy is effective and safe for the treatment of lymphedema patients.

CONCLUSION

The two trials included in this review both have their limitations and have yet to be replicated, so the results must be viewed with caution. There is weak evidence to support the use of US or electrotherapy in the treatment of breast cancer related lymphedema. Moreover, determination of the relationship between these therapies and the risk of metastasis would require longer patient follow-up times. In these two studies, the use of US or electrotherapy in the treatment of chronic upper limb breast cancer-related lymphedema did not result in significant lymphedema reduction. There was a marginally significant reduction of pain after TENS therapy. Therefore, there is insufficient evidence for recommendation.

Trials of complex physical therapy programs are not easy to conduct, but still possible. Moreover, the potential for safely maximizing the positive outcomes of breast cancer rehabilitation through the use of appropriate rehabilitation techniques presents an opportunity for involving physiatrists and the rehabilitation team in the care of cancer patients. There is a clear need for well-designed randomized trials to address the use of physical modalities in the treatment of breast cancer-related lymphedema.

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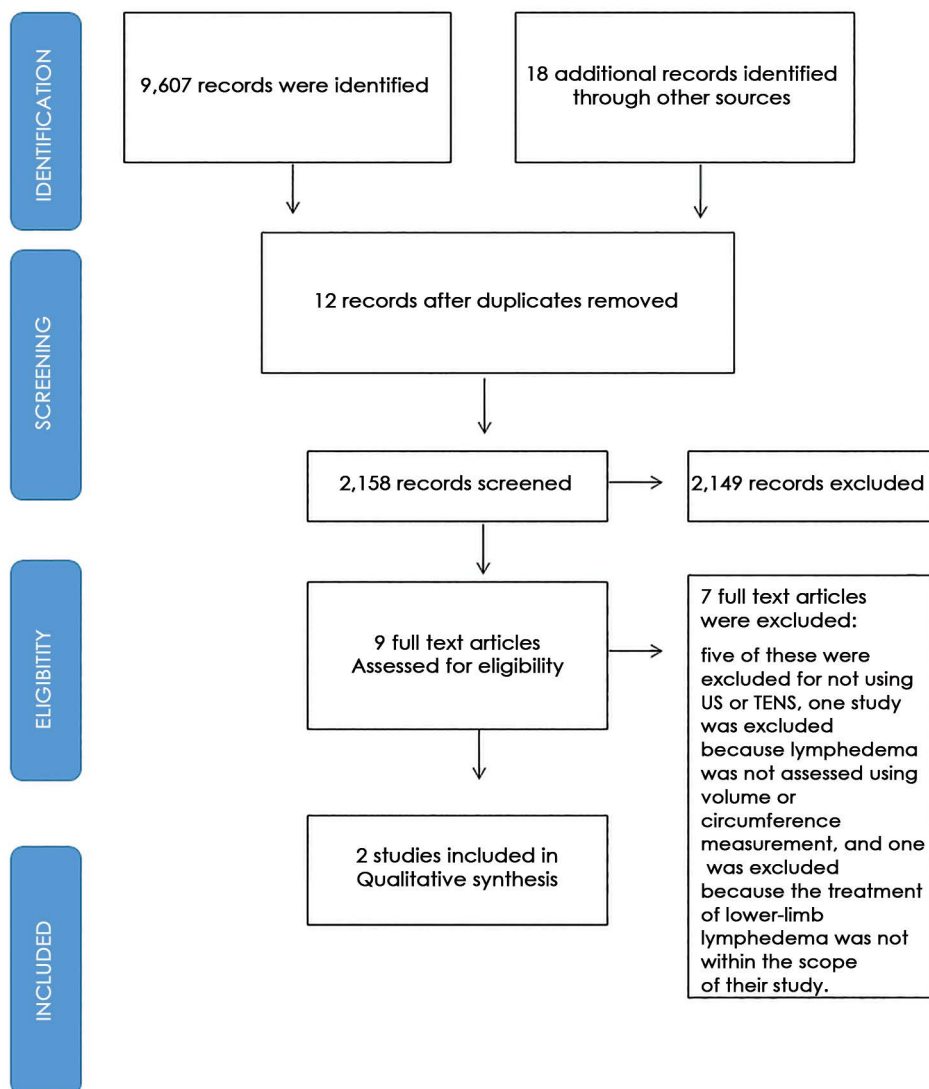


Figure 1. Flow diagram