

Mesenchymal stem cell therapy for breast cancer-related secondary lymphedema (Review)

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Abstract. Secondary lymphedema, affecting ~15-30% of patients who survive breast cancer, is a common consequence following treatment. At present, there is no gold standard for the treatment of breast cancer-related lymphedema (BCRL). Conventional methods such as physiotherapy and surgery demonstrate a limited effectiveness in mitigating lymphatic swelling or discomfort and fail to provide substantial physiological improvement or a definitive cure for lymphedema. However, stem cell therapy has garnered notable attention due to its regenerative potential and its capacity to modulate inflammatory processes. Mesenchymal stem cell (MSC) therapies exhibit promise in ameliorating BCRL by addressing edema, promoting lymphangiogenesis and mitigating fibrosis. It is shown that MSC therapy promotes the regeneration of autologous lymphatic networks and improves vascular conditions in rodent tail and hindlimb lymphedema models, which offers relief from lymphedema symptoms including limb volume asymmetry and impaired lymphatic drainage. However, currently, due to a lack of a universally recognized or standardized treatment regimen for BCRL, there is a need for additional clinical studies featuring larger sample sizes and extended follow-up periods to further investigate this prospective therapeutic modality. The present review aims to provide

guidance for further research and therapeutic interventions following the results observed in both preclinical and clinical settings. The present study investigated the pathogenesis of secondary lymphedema, previous advancements in stem cell therapy for this condition and an analysis of persisting challenges.

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1. Introduction

Secondary lymphedema is a chronic progressive disease characterized by the abnormal accumulation of interstitial fluid and tissue swelling (1). Its core pathological mechanism is due to the structural or functional damage of the lymphatic drainage system. Such damage is often caused by tumor treatments (such as axillary lymph node dissection and radiotherapy for breast cancer), parasitic infections (such as filariasis) or trauma (2). The clinical manifestations include asymmetric swelling of the limbs, fibrosis and recurrent infections. In severe cases, it can progress to lymphangiosarcoma or limb dysfunction, notably impairing the quality of life of patients (3). Among them, breast cancer-related lymphedema (BCRL) accounts for 20-65% of secondary cases (4). Its risk factors include the use of taxane, obesity and radiotherapy to regional lymph nodes at doses exceeding 50 Gy (5-7). A global cancer statistic shows that breast cancer ranks first in the incidence of female malignant tumors (accounting for 24.5% of newly diagnosed cancer cases) (8,9). Reported incidence rates range from 6.7-62.5% depending on surgical and radiotherapy protocols (10,11). However, modern techniques such as sentinel lymph node biopsy and immediate lymphatic reconstruction have reduced the risk to 5-10 and 7.0%, respectively (12,13). BCRL is still a problem that should be solved in the field of cancer rehabilitation.

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Abbreviations: BCRL, breast cancer-related lymphedema; VEGF-C, vascular endothelial growth factor C; CCR, C-C chemokine receptor; MSCs, mesenchymal stem cells; MTT, mean transit time; BMSC, bone marrow stem cell; CDT, complex decongestant physical therapy; LYVE-1, lymphatic vessel endothelial receptor-1; LECs, lymphoendothelial cells; PRP, platelet-rich plasma; EV, extracellular vesicle

Key words: BCRL, lymphangiography, MSCs, regulatory T cells

Currently, the management of BCRL faces a twofold challenge: i) An absence of standardized assessment tools; and ii) limitations of treatment methods. Although the International Society of Lymphology has proposed a staging system based on clinical symptoms (such as the subclinical stage or lymphostatic elephantiasis), it is subjective and unable to quantify the degree of fibrosis (3). While bioimpedance spectroscopy and 3D imaging techniques [such as near-infrared fluorescence lymphatic imaging with 3D reconstruction (14,15), high-resolution volumetric analysis (15) and multiparametric MRI-based radiomics (16,17)] can enhance the sensitivity of early detection, standardized imaging protocols are lacking and are device-dependent, which make it difficult to popularize (3,9). In terms of treatment, conservative therapies (such as compression therapy and manual lymphatic drainage) can relieve symptoms, but their efficacy is limited for advanced fibrosis (18,19). Surgical interventions (such as lymphatic-venous anastomosis and liposuction) can improve the appearance, but they have risks such as damage to residual lymphatic vessels, aesthetic deformities and the formation of unstable scars (20-22). In this context, mesenchymal stem cell (MSC) therapy is a focus of research due to its unique dual mechanisms of tissue repair and immunomodulation (23). MSCs promote lymphangiogenesis by paracrine-secreting factors such as vascular endothelial growth factor C (VEGF-C) and stromal cell-derived factor 1 α . Additionally, they inhibit the release of proinflammatory factors such as TNF- α and IL-6, which alleviates fibrosis (24,25).

In the present review, the pathophysiological mechanisms of BCRL, which are the foundation for understanding the disease, were investigated. Subsequently, MSC therapy, with its advantages and disadvantages as a treatment for secondary lymphedema, in the context of BCRL in particular, was evaluated. Finally, the present study summarized and appraised the relevant animal and clinical experiments on various stem cell therapies for secondary lymphedema, including those associated with BCRL. Through this process, the present review aimed to assess the progress made and the problems yet to be solved in this field.

2. Pathophysiological mechanism of BCRL

The physiological function of lymphatic vessels is to facilitate the exchange of materials such as proteins, lipids and water between tissue stroma and blood vessels. Its unique structure enables the transportation of macromolecular proteins, lipids and a notable volume of tissue fluid into lymph fluid, which are typically challenging to transfer through the venous system (26). A number of patients with cancer undergoing radiotherapy and chemotherapy may experience lymphatic vascular insufficiency and impaired drainage due to specific therapeutic agents [for example, doxorubicin decreases the lymphatic pumping frequency (27)] and physical factors [for example, radiation-induces axillary fibrosis at doses >50 Gy (28)]. Additionally, to maintain the normal function of lymphatic vessels, the pressure within the vessels should be kept ≤ 0 mm H₂O, as elevated intraluminal pressure disrupts cytoskeletal dynamics and impairs fluid drainage. This is evidenced by studies on lymphatic biomechanics and pathological conditions such as lymphedema (29-31). Surgical

interventions often disrupt axillary lymphatic outflow and cause lymphatic blockage (32), leading to a notable increase in lymphatic pressure. This increased pressure within the lymphatic system affects the transport of proteins and immune cells, resulting in the accumulation of protein-rich fluids in the extracellular matrix and triggering an inflammatory response (Fig. 1).

Previous studies demonstrate an increase in the number of CD4⁺ T cells and their differentiation into T helper (Th) type 2 (Th2) cells in lymphedema mouse models (33-35). Inflammation-induced CD4⁺ T cells stimulate the expression of VEGF-C, which drive lymphatic vessel proliferation in tissues (36). After lymphatic damage, M2 macrophages secrete VEGF-C and function as lymphoendothelial progenitor cells. Dendritic cells are activated at the injury site and migrate into lymphatic vessels along the concentration gradient of chemokine C-C motif ligand (CCL)21, which they themselves secrete. Activated dendritic cells then travel to lymph nodes, where they activate Th cells (37). Activated Th cells express surface markers such as cutaneous lymphocyte-associated antigen, C-C chemokine receptor (CCR)4, CCR9 and CCR1. Guided by adhesion molecules and CCLs, activated Th cells infiltrate the injured site and release inflammatory cytokines, including IFN- γ , TNF- α , IL-4 and IL-5, which collectively orchestrate immune responses and tissue remodeling (38-40). A prolonged inflammatory response can lead to tissue remodeling, which is characterized by increased collagen deposition, excessive growth of fat and connective tissue (37). Recruitment of various immune cells, including M2 macrophages, Th2 lymphocytes and neutrophils, promotes fat deposition and fibrosis in lymphedema (41-43). In the chronic phase, there is low-grade inflammation, fibrosis, fat deposition and non-functional lymphangiogenesis, which is characterized by valve defects and systolic dysfunction.

3. Evaluation and grading of BCRL

Lymphography-assisted stem cell therapy represents a novel approach for treating secondary lymphedema, offering benefits such as quantifying the severity of lymphedema and enhancing diagnostic accuracy. A study by Peña Quián *et al* (44) conducts multiple shallow and deep stem cell injections in the lymphatic vessel trace and groin region of 2 patients with chronic lower limb lymphedema, in order to evaluate the anatomical structure and function of the lymphatic system. The study demonstrates that after stem cell implantation, imaging reveals the presence of new lymphatic branches not observed before treatment, along with thicker radioactive columns. Additionally, patients exhibit an increase in dermal reflux and proximal lymph node activity, suggesting improved lymphatic drainage.

The study by Toyserkani *et al* (45) quantitatively assesses lymphatic drainage by measuring the mean transit time (MTT) in patients with BCRL before and 12 months after injection of adipose-derived regenerative cells. The study notes no notable change in MTT in the lymphedema group before and after treatment, which contradicts the findings of Peña Quián *et al* (44), the only previous report of lymphography after stem cell therapy. Subsequently, using indocyanine green lymphangiography, the study by Jørgensen *et al* (46) assesses lymph vessels in real time in 237 patients with BCRL.

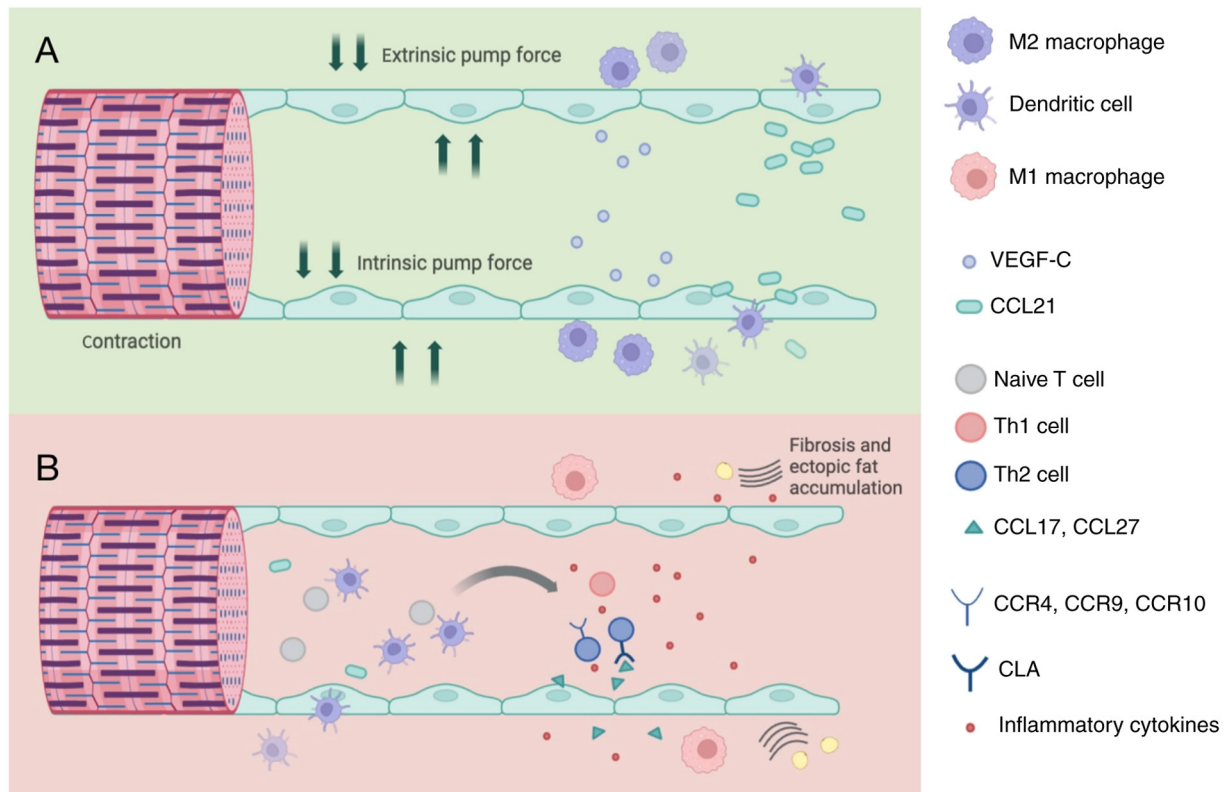


Figure 1. Formation of lymphedema after lymphatic injury. (A) Lymph flow is facilitated by the intrinsic pump force of the lymphatic vessels, along with the extrinsic pump force generated by skeletal muscles. Following lymphatic damage, such as that caused by surgical resection (for example, lymph node dissection) or radiation therapy in cancer treatments, M2 macrophages and dendritic cells become activated. (B) Activated dendritic and Th cells infiltrate the damaged area and secrete cytokines such as IL-2 and TNF- α . VEGF-C, vascular endothelial growth factor C; CCL, CC chemokine ligand; Th, T helper; CCR, C-C chemokine receptor; CLA, cutaneous lymphocyte-associated antigen.

This approach offers prospective treatment and validates the reliability and safety of this technique for staging BCRL. It provides disease-related information that cannot be obtained by clinical measurements alone (46). Despite facing challenges such as poor spatial resolution and inadequate quantification, lymphatic imaging technology remains the gold standard for assessing the extent of lymphatic dysfunction and is pivotal in determining treatment strategies.

4. MSC therapy for BCRL

MSCs, as pivotal tools in regenerative medicine, vary in biological traits and therapeutic effects by tissue source. In secondary lymphedema management, bone marrow-derived MSCs (BMSCs) and adipose-derived MSCs (ADSCs) demonstrate distinct clinical profiles. Regarding proliferative capacity, BMSCs show notable donor age-dependent limitations *in vitro* expansion, whereas ADSCs obtained through minimally invasive lipoaspiration maintain superior passage stability (47). Differentiation analyses reveal that BMSCs possess enhanced osteochondral differentiation potential mediated by constitutive activation of the Wnt/ β -catenin pathway within their native bone marrow niche (48). By contrast, ADSCs have adipogenic lineage predisposition while demonstrating unique therapeutic value in ischemic tissue repair through robust secretion of angiogenic factors, such as VEGF (49). Safety evaluations indicate a comparable absence of severe adverse events

between both cell types; however, the immunogenic risk is notably reduced for ADSCs in allogeneic transplantation due to their human leukocyte antigen-DR isotype-negative phenotype (50).

Over the past decade, there have been a number of reports on MSC-based treatments for lymphedema in both animal studies and clinical trials (Fig. 2; Tables I and II). In the animal studies, lymphedema models are predominantly established using mouse posterior limbs and tails (51-53). Evaluating the treatment outcomes involves immunohistochemical staining methods such as perimeter measurements, depth of skin edema, imaging techniques, anti-CD31 staining for angiogenesis, anti-lymphatic vessel endothelial receptor-1 (LYVE-1) staining for lymphangiogenesis and staining for VEGF receptor expression levels. Additionally, no notable adverse events associated with MSC transplantation were observed in the clinical trials analyzed in the present review.

Application of BMSC therapy. In a randomized controlled trial involving 50 Chinese patients with lymphedema following breast cancer surgery (54), quantitative analysis reveals that BMSC transplantation achieves an improved long-term cure result compared with complex decongestant therapy (CDT). At a 12-month follow-up, the BMSC group demonstrates a 78.5% reduction in mean limb edema volume (vs. 54.5% in CDT) and an 82% decrease in visual analog scale pain scores (vs. 60% in CDT).

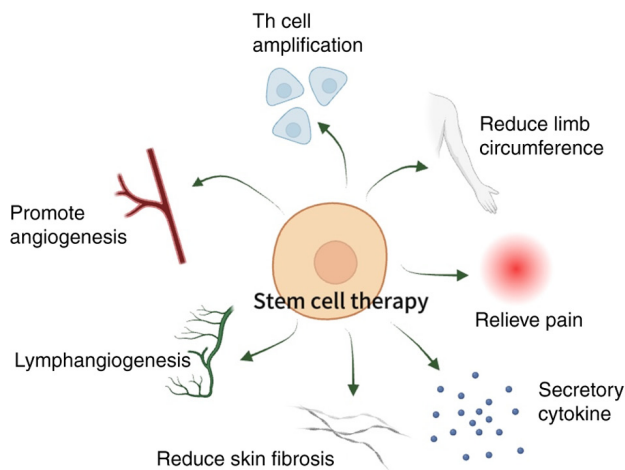


Figure 2. Stem cell transplantation improves lymphedema. Stem cell transplantation can improve the symptoms of lymphedema including promoting Th cell amplification, angiogenesis and lymphangiogenesis, reducing limb circumference and skin fibrosis, relieving pain, and secreting regenerative cytokines such as vascular endothelial growth factor C and hepatocyte growth factor. Th, T helper.

In a subsequent mechanistic study by Zhou *et al* (55) using rabbit models indicates that BMSC transplantation combined with VEGF-C in the treatment of limb lymphedema is more effective compared with stem cells alone. Additionally, the study quantifies the synergistic effect of the BMSC/VEGF-C combination therapy. After 28 days of treatment, the limb volume of the dual treatment group reduces by $58.4 \pm 7.1\%$ vs. $38.4 \pm 5.7\%$ of the BMSC treatment group alone, and this advantage is maintained at the 6-month follow-up. Furthermore, the study observes an increase in both blood vessel density and lymphatic vessel density in the combined treatment group. These structural enhancements may translate into lymphoscintigraphy, demonstrating accelerated lymphatic clearance, a functional parameter not evaluated in this investigation (55). In a clinical cohort of 40 patients with chronic lymphedema (56), BMSC mononuclear cell therapy achieves a clinically notable ankle circumference reduction after 6 months, which is supported by immunohistochemical evidence of enhanced lymphatic vasculature. Conversely, physical therapy controls reveal no measurable structural improvement and limited functional benefits.

Previously, a number of studies have attempted to apply the arteriovenous ring technique to lymphatic tissue engineering (57–59). Robering *et al* (60) combine human lymphoendothelial cells (LECs) and BMSCs into the fibrin matrix surrounding the atrioventricular ring, and demonstrate preliminary progress in the culture of human lymphatic blood vessels in rats, providing a possible way to generate transplantable lymphatic blood vessel networks.

Application of ADSCs. A 2013 transcriptomic analysis (61) reveals notable functional divergence in ADSCs from lymphedematous vs. healthy tissues. Lymphedema-associated ADSCs exhibit an 8-fold increase in the peroxisome proliferator-activated receptor- γ expression levels and a 2-fold decrease in VEGF secretion under angiogenic conditions.

A study by Dhumale *et al* (62) also reveals this pathophysiological reprogramming, which confirms the proangiogenesis and parasecretory effects of human ADSCs. The study further indicates that such effects are mainly associated with CD31⁺ enrichment within this cell population.

In addition to the lymphangiogenic effects of VEGF-C, evidence delineates platelet-mediated regenerative pathways. In a murine tail lymphedema model, ADSCs/platelet-rich plasma (PRP) combination treatment increases the mean surface area of anti-LYVE-1-stained lymphatic vessels at 2 weeks by $4.1 \pm 1.0\%$, nearly a 2-fold increase compared with ADSC only therapy groups ($2.5 \pm 0.3\%$). In addition, PRP treatment shows the best results regarding a reduction in wound size and improving wound epithelialization, with less of an increase in wound perfusion (25.1 ± 31 PU vs. 33.8 ± 33 PU in the ADSCs only group) (63). In a subsequent study, Hayashida *et al* (64) demonstrates that the number of LYVE-1 immunoreactive lymphatic vessels in a lymphedema mouse model undergoing ADSC transplantation notably increases when using indocyanine green lymphatic vessel imaging. The mechanism study by Ogino *et al* (65) further reveals that after 2 weeks of ADSCs transplantation, the proliferative lymphatic vessel ratio increases by $0.61 \pm 0.04\%$, recovers the orientation of type I collagen fibers from parallel to random and increases the number of type III collagen fibers. A study by Dai *et al* (66) further divides ADSCs into those expressing podoplanin and those not expressing podoplanin. In a mouse model of limb lymphedema, transplantation of podoplanin-positive ADSCs resulted in a notable generation of lymphatic vessels and remission of lymphedema, compared with both the podoplanin-negative ADSCs and the unsorted ADSC population (the original, heterogeneous cell mixture from which the podoplanin-positive and -negative subpopulations were isolated). The study reveals a large number of lymphangiogenic cytokines such as VEGF-C and D in the podoplanin-positive supernatant, which are absent in the podoplanin-negative and unclassified groups. Furthermore, immunocolocalization reveals that podoplanin-positive cells in lymphatics are LYVE-1 positive.

In a randomized controlled trial by Jørgensen *et al* (67), 34 patients that survived breast cancer with secondary lymphedema were enrolled, with 10 patients (71.4%) completing a 4-year follow-up after receiving ADSCs therapy combined with axillary scar release. In the study, ADSCs are isolated from autologous abdominal or thigh liposuction aspirates, with a mean cell count of 2.2×10^5 cells/ml per injection. Quantitative assessments reveal that 60% of treated patients achieve $\geq 50\%$ reduction in self-reported lymphedema-related symptoms measured by the disabilities of the arm, shoulder and hand questionnaire, with notable improvements in upper extremity function scores. Additionally, 6 patients (60%) down staged the lymphedema treatment on their own initiative. The 4-year survival analysis demonstrates no evidence of locoregional recurrence, with only 2 cases of distant metastasis unrelated to treatment. These findings suggest that ADSC-based interventions provide clinically meaningful symptomatic relief and functional improvement in patients with post-mastectomy lymphedema, warranting further large-scale randomized trials with standardized outcome metrics.

Table I. Stem cell-based therapy of lymphedema in animal studies.

First author, year	Animal used	Edema site	Type of cells used	Number of animals used	Treatment	Outcomes	(Refs.)
Zhou <i>et al</i> , 2011	New Zealand white rabbits (weight, ~2.5 kg)	Right hind limb	BMSCs from New Zealand white rabbits.	n=NM (four groups)	BMSCs (1×10^7 cells) or/and VEGF-C (150 ng/kg body weight; Bio Vision, Inc.; Abcam) in 2 ml DMEM are intramuscularly injected into irradiated and surgically traumatized areas (0.1 ml each point) using a 1 ml needle	BMSC and VEGF-C monotherapy induces lymphangiogenesis and ameliorates the lymphedema. The combination of BMSC transplantation and VEGF-C infusion improves the treatment of secondary lymphedema.	(55)
Hayashida <i>et al</i> , 2017	Male C57BL/6J mice (10-weeks-old)	Hind limb	ADSCs from mice.	n=20 (four groups)	ADSCs (1×10^4) are injected with 0.3 ml PBS. Each solution is injected subcutaneously after surgery using a 30-gauge needle into the entire ipsilateral left abdominal cutaneous flap, proximal (to the flap) limbs and distal (to the flap) limbs.	Using a combined treatment of ADSCs and vascularized lymph node transfer, the percentage improvement increases while the percentage deterioration decreases compared with the control, vascularized lymph node transfer group, ADSCs and no-vascularized lymph node transfer group. The number of lymphatic vessels with LYVE-1 immunoreactivity markedly increases in mice treated with ADSCs, and the B16 melanoma cells only metastasize in groups that are treated by day 28 with vascularized lymph node transfers.	(64)
Ogino <i>et al</i> , 2020	Male C57BL/6J mice (5-6-weeks-old).	Left hind limb.	ADSCs from C57BL/6J mice.	n=18 (three groups)	ADSCs (7.5×10^5) are injected into each mouse with 0.3 ml cell preservative solution (CELLBANKER 2; Zenoaq	ADSC transplantation promotes LEC proliferation, increases the number of lymphatic vessels, increases	(65)

Table I. Continued.

First author, year	Animal used	Edema site	Type of cells used	Number of animals used	Treatment	Outcomes	(Refs.)
Dai <i>et al.</i> , 2020	Female C57BL/6J mice (6-8-weeks-old)	Hind limb	ADSCs isolated from C57BL/6J green fluorescent protein-transgenic female mice (20-23 g; 4 weeks old).	n=15 (three groups)	Resource Co., Ltd.). Each solution is injected subcutaneously 24 h after surgery using a 27-gauge needle into the distal (to the incised area) limbs and proximal limbs. Each animal is treated with 2×10^6 cells in $100 \mu\text{l}$ of saline. After initial injury, cell implantation is carried out once every 2 weeks until week 16.	wound healing, decreases dermal fibrosis and increases lymphatic vessel dilation capacity. Implanted cells promote lymphangiogenesis, with the most notable effect observed in the podoplanin-positive group. Immunocolocalization further reveals that the podoplanin-positive cells in the lymphatic vessels are positive for LYVE-1.	(66)
Tashiro <i>et al.</i> , 2023	Female C57BL/6J mice (10-weeks-old).	Bilateral hind limbs	EVs derived from human ADSCs and embryonic kidney 293T cells.	n=NM (three groups)	Injection of PBS or ADSC-EVs ($\sim 40 \mu\text{g}$) or 293T-EVs ($\sim 40 \mu\text{g}$) as a thin layer in the whole leg, carried out on postoperative days 7 and 14	ADSC-EVs decreases hind limb lymphedema <i>in vivo</i> . ADSC-EVs increases lymphangiogenesis and angiogenesis and decreases fibrosis in the lymphedema limb.	(70)

ADSCs, adipose-derived stem cells; LYVE-1, lymphatic vessel endothelial receptor-1; LEC, lymphatic endothelial cells; EVs, extracellular vesicles; 293T-EVs, EVs derived from human embryonic kidney 293T cells; NM, not mentioned; BMSCs, bone marrow stem cells; VEGF-C, vascular endothelial growth factor C.

Table II. Stem cell-based treatment of patients with lymphedema.

First author, year	Study type	Edema site	Number of patients	Type of cells used	Treatment	Valuation criteria	Outcomes	Follow-up	(Refs.)
Hou <i>et al</i> , 2008	Randomized controlled clinical trial.	Upper limb	n=50 (BMSC group, 15 patients; CDT group, 35 patients).	Autologous BMSCs (diagnostic bone marrow aspiration with bone marrow hyperplasia active).	Injection sites are 1 cm away from each other and the needle is placed into the muscles of the thorax or subcutaneous tissue. In one injection site, 0.5 ml BMSC is injected.	Arm volume ^a ; pain in arm and/or chest ^b	Patients in the BMSC group and CDT group demonstrate a reduction in lymphedema volume and pain scale; however, the duration of the improvement is increased in the patients in the BMSC group compared with the patients in the CDT group.	After 1, 3 and 12 months.	(54)
Toyserkani <i>et al</i> , 2019	Prospective, open-label, single-arm and single-center feasibility and safety study.	Upper limb.	n=10	Autologous ADSCs	To release axillary scar tissue, 28.1±7.8 ml of fat/patient are injected ~2 h before the transplantation of 5 ml of 5.37±1.08x10 ⁷ ADSCs/patient, which is subcutaneously injected into the axilla at eight points around the scar.	Arm volume; DXA scans; discomfort (redness, swelling, itching, pain and infection)	No notable reduction in volume; however, 50% of patients reduced their use of conservative management ^c .	After 1, 3, 6 and 12 months.	(45)

Table II. Continued.

First author, year	Study type	Edema site	Number of patients	Type of cells used	Treatment	Valuation criteria	Outcomes	Follow-up	(Refs.)
Ehyaeeghodraty <i>et al</i> , 2020	Single-center, prospective, non-randomized clinical trial.	Lower limb.	n=10.	Autologous PBMCs, collected from the blood of the antecubital vein after subcutaneous injections of G-CSF (300 µg/day) for 4 days.	Each patient receives a subcutaneous injection, several hours after the collection of PSMCs and again 3 weeks later, of 1 ml/site 9.5±6.8x 10 ⁸ PBMCs into 80 marked squares on the affected lower limb (below the knee to above the ankle).	Limb volume; limb circumference; lymphnode biopsy ^d ; lymphoscintigraphic transport index ^e ; quality of life ^f .	The volume of the lower limbs decreased, the quality of life increased, the lymphoscintigraphic transport index increased and tissue samples increased in the lymphatic vessels in 60% of the patients compared with before treatment.	Once a month for 6 months.	(85)
Jørgensen <i>et al</i> , 2021	Prospective open-label, single-arm and single-center phase I study.	Upper limb.	n=10.	Autologous ADSCs.	ADSCs are injected in eight 0.5 ml doses (total of 4 ml) using a 25-gauge cannula in predefined points in the axilla adjacent to the axillary scar, in the same area and depth where fat grafting was carried out.	Arm volume; safety ^g ; lymphedema symptoms; quality of life; lymphedema-associated cellulitis; conservative treatment use ^h .	No notable decrease in BCRL volume. Improvement in the self-reported upper extremity disability, arm heaviness and tension.	After 1, 3, 6, 12, and 48 months.	(67)

^aArm volume is calculated by measuring circumferences at 4-cm intervals (wrist to shoulder) and estimating volume via cylinder formula. Data show post-treatment vs. pre-treatment volume differences and affected- unaffected arm volume gaps to assess edema resolution. ^bPatients quantify their pain on a numerical scale from 0 to 5, with 0 being no pain at all and 5 being severe, constant pain. ^cPatients use a compression sleeve, compression gauntlet, night compression or pneumatic compression device to treat their lymphedema. The average frequency that the patients used each treatment (daily, >3 days/week, 1-3 days/week or <1 day/week) was compared before and after treatment. CDT, complex decongestive physiotherapy; DXA, dual-energy X-ray absorptiometry; G-CSF, granulocyte colony-stimulating factor; PBMC, peripheral blood mononuclear cell; BMSC, bone marrow stem cells; ADSCs, adipose-derived stem cells; BCRL, breast cancer-related lymphedema. ^dLymphatic endothelial cells are stained brown using immunohistochemistry with D2-40 to calculate the mean lymphatic vessel number. ^eLymphoscintigraphic transport index, ranging from 0 (healthy vessels) to 45 (severe lymphatic disturbance). This index provides a quantified assessment of lymphatic drainage and relies on lymphatic transport kinetics, distribution pattern, lymph node appearance time and the appearance of lymph nodes and vessels. ^fPatients completed the World Health Organization quality of life questionnaire, which is scored between 26 and 130. ^gNo serious adverse events were found in the phase I study after 4-years of follow-up. Out of a total of 34 patients, only 1 patient was diagnosed with early-stage contralateral breast cancer 10 months after treatment, and 1 patient was diagnosed with a distant recurrence of primary breast cancer 42 months after treatment. No cases of locoregional breast cancer occurred.

Recent studies in extracellular vesicle (EV) therapeutics demonstrate the superior efficacy of ADSC-derived EVs compared with conventional therapeutic approaches [such as the transplantation of intact ADSCs and standard decongestive therapy (including manual lymphatic drainage, compression bandaging and exercise)] in promoting lymphatic regeneration and reducing edema volume in secondary lymphedema management (68-70). The potential oncogenic risk of EV treatment is reduced compared with direct stem cell transplantation, as ADSC-EVs lack cellular replication capacity and exhibit targeted delivery of therapeutic cargo without promoting tumor proliferation or metastasis in preclinical models (70-72). The previous study reveals that ADSCs-EV can promote the proliferation and migration of LECs and enhance lymphatic formation. In murine models, EV treatment achieves a $65.1 \pm 4.5\%$ limb volume reduction at 4 weeks post treatment, with an increase in the total number of LYVE-1-positive lymphatic vessels ($25.3 \pm 5.2\%$ vs. $16.1 \pm 2.8\%$ in controls) (70). Mechanistically, an analysis of mRNA expression levels reveals a 2-fold enrichment of lymphangiogenic markers such as VEGF-C, prospero-related homeobox 1 (Prox1), LYVE-1 and podoplanin, in an EV treatment group compared with a PBS treatment group (73-75).

Other cell-based treatments. In addition to BMSCs and ADSCs, other cell populations associated with stem cells have also been considered for the treatment of secondary lymphedema.

A study by Kawai *et al* (76) tried to treat secondary lymphedema with human LECs transplantation and achieved certain results. LECs extracted from the normal dermis of patients with breast cancer were transplanted into a rat model of caudal lymphedema. While this local injection did not ensure the long-term survival of LECs, in the short term, the skin of the rat tail in the podoplanin-positive purified LECs transplantation group became thinner, and evidence of lymphatic vessel regeneration from the rats was observed. A study by Deng *et al* (77) demonstrates that lentiviral-mediated Prox1 overexpression in human ADSCs enables stable differentiation into lymphoendothelial-like cells. By transfecting human ADSCs with Prox1-encoding vectors, sustained lymphatic differentiation was established, which was confirmed via flow cytometry, reverse transcription-quantitative-PCR, protein quantification and immunofluorescence analyses, notably increasing the protein levels of podoplanin, LYVE-1 and VEGFR3 (2 weeks post-differentiation). This genetic modification maintained lymphoendothelial characteristics while bypassing transient differentiation patterns observed in non-engineered counterparts.

In addition to the application of LECs, BMSCs also expand regulatory T cells (Tregs) *in vitro* and *in vivo* studies (72,78,79), and Treg induction may serve a positive role in stem cell transplantation in the treatment of lymphedema (80). Furthermore, intense inflammatory response and immune cell infiltration serve an important role in the pathogenesis of secondary lymphedema. A study by Gousopoulos *et al* (81) quantifies this axis in murine lymphedema models and reveals that a depletion of CD4⁺ T cells (shown via anti-CD4 antibodies) results in a notable reduction of the tissue area that is covered by lymphatic

vessels. Furthermore, IL-2/anti-IL-2 complex-induced Treg expansion achieves edema reduction with a decrease in the CD45⁺, CD206⁺ and CD68⁺ infiltrates. Adoptive transfer of splenic Tregs decreases dermal TGF- β 1, reduces collagen deposition (shown with Sirius Red staining) without altering VEGF-C levels and increases the fluorescence intensity of the lymphatic-specific tracer (82-84).

Additionally, other studies investigate the utilization of autologous peripheral blood stem cell transplantation as a treatment for primary lymphedema (85,86). A clinical study involving 10 patients reveal that this treatment can improve edema symptoms to an extent (85); however, further high-quality clinical studies are required to verify its effectiveness and scope of application.

5. Discussion

BCRL is predominantly induced by radical surgery, radiotherapy and cytotoxic chemotherapy, and manifests in 20% of patients with upper extremity, thoracic or breast involvement (87). The emerging therapeutic potential of MSCs in degenerative, autoimmune and genetic disorders has extended to lymphedema management. BMSCs demonstrate therapeutic efficacy through paracrine-mediated lymphangiogenic properties that facilitate damaged network reconstruction. However, their clinical implementation is constrained by invasive harvesting procedures and age-dependent proliferative decline (88-90). By contrast, ADSCs exhibit superior proangiogenic capabilities via elevated VEGF secretion, coupled with minimally invasive harvesting procedures, demonstrating enhanced ischemic tissue revascularization and lymphatic remodeling in preclinical models. However, the adipogenic tendency of ADSCs may increase the risk of post-transplant fat deposition (91). The present review suggests that the selection of the MSCs source is optimized according to BCRL heterogeneity and pathological stage (acute edema/chronic fibrosis), and that the synergistic effects of multi-source MSCs combination therapies is investigated.

While MSCs exhibit therapeutic potential in autoimmune diseases and chronic inflammation through their immunomodulatory properties and paracrine effects, their clinical application presents a complex duality of advantages and risks that requires examination. A prominent limitation is their unpredictable differentiation behavior (92). As a study by Yoon *et al* (93) demonstrates, transplanting MSCs may form ectopic tissues due to microenvironmental cues, where BMSCs without immunophenotypic purification (for example, those that lack CD105 $\square$, CD90 $\square$ or CD73 $\square$) cause myocardial calcification instead of functional repair. Furthermore, their dual role in oncology is also concerning. While MSCs can inhibit tumors via immune modulation (94), they may paradoxically promote tumor progression by suppressing natural killer/CD8⁺ T cell activity, polarizing Th2 responses and stimulating angiogenesis (95). Such contradictions highlight the need for further mechanistic studies to reconcile the regenerative benefits of MSCs with their pathological risks.

Current animal models for BCRL successfully mimic localized swelling but fail to recapitulate the inflammatory tumor microenvironment, which obscures the risks

associated with MSC therapies. Cancer exerts an influence on the immune response through the release of various factors, such as cytokines and chemokines, and these factors have the capacity to modify the capability of the immune system to recognize and eliminate cancer cells (96). Limitations in animal lifespans and experimental durations restrict long-term safety evaluations, especially for delayed tumorigenic effects. By contrast, clinical trials observe no MSC-triggered cancer recurrence or metastasis in cases with BCRL. ADSCs, prioritized for their availability, ethical compliance and trophic factor release, show clinical potential. However, their inherent tumor tropism and unaddressed chronic safety issues emphasize the necessity to balance regenerative benefits against oncological hazards during therapeutic development.

Although MSCs demonstrate therapeutic efficacy in clinical trials through tissue regeneration and immunomodulation, their clinical translation remains hindered by unresolved biological risks such as uncontrolled differentiation and unclear long-term safety (97,98). While MSC-derived exosomes show reduced oncogenic concerns compared with whole-cell therapies, several trials have yielded favorable clinical outcomes, showcasing both safety and efficacy (99–101). Previous studies highlight MSCs transplantation safety in short-term applications, yet gaps in the understanding of chronic inflammatory responses, genomic instability and tumor microenvironment interactions remain. To advance MSC-based therapies, further studies are imperative, in which direct comparisons of their regenerative benefits against latent pathological risks should be prioritized.

6. Conclusions

MSC therapies exhibit promise in ameliorating BCRL by addressing edema, fostering lymphangiogenesis and mitigating fibrosis. However, due to the absence of a universally recognized or standardized treatment regimen for BCRL, additional clinical studies with larger sample sizes and extended follow-up periods are required to further investigate this prospective therapeutic modality.

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Authors' contributions

YZ, JC and FL designed, guided and modified the present study and manuscript. SH conducted the study, wrote the manuscript and collected and collated the data. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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