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## Application and prospect of adipose stem cell transplantation in treating lymphedema

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### Abstract

#### BACKGROUND

Lymphedema is a chronic, debilitating and incurable disease that affects 0.13%-2% of the global population. Emerging evidence indicates that adipose-derived stem cells (ADSCs) might serve as suitable seed cells for lymphatic tissue engineering and lymphedema therapy.

#### AIM

To summarize applications of ADSCs for treating lymphedema in both animal studies and clinical trials.

#### METHODS

A systematic search was performed on four databases – PubMed, Clinicaltrials.gov, the evidence-based Cochrane Library, and OVID – using the following search string: (“lymphedema” or “lymphoedema” or “lymphangiogenesis”) and (“adipose-derived stem cells” or “adipose-derived stromal cells” or “adipose-derived regenerative cells”). A manual search was performed by skimming the references of relevant studies. Animal studies and clinical trials using adipose-derived cells for the treatment of any kind of lymphedema were included.

#### RESULTS

A total of eight research articles published before November 2019 were included for this analysis. Five articles focused on animal studies and another three focused on clinical trials. ADSC transplantation therapy was demonstrated to be effective against lymphedema in all studies. The animal studies found that coadministration of ADSCs and controlled-release vascular endothelial growth factor-C or platelet-rich plasma could improve the effectiveness of ADSC therapy.

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Three sequential clinical trials were conducted on breast cancer-related lymphedema patients, and all showed favorable results.

## CONCLUSION

ADSC-based therapy is a promising option for treating lymphedema. Large-scale, multicenter randomized controlled trials are needed to develop more effective and durable therapeutic strategies.

**Key words:** Lymphedema; Adipose-derived stem cells; Animal model; Clinical trial; Vascular endothelial growth factor-C; Lymphangiogenesis

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**Core tip:** Lymphedema is a growing global health problem. Adipose-derived stem cells might serve as suitable seed cells for tissue engineering of lymphatic vessels *in vitro* and *in vivo*. A systematic search of publications on the application of adipose-derived stem cells in the treatment of lymphedema identified five animal studies and three clinical trials. All eight studies showed improvement of lymphedema after treatment with adipose-derived stem cells. Animal studies conducted with acute lymphedema mouse models provided data for finding the proper dose and methods of administration. Clinical trials were conducted on breast cancer-related lymphedema patients and are important references for further application.

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## INTRODUCTION

As the second circulatory system of the body, the lymphatic system functions to transport tissue fluid in the interstitial space back to the venous circulation system and maintain fluid homeostasis. Hypoplasia or dysfunction of lymphatic vasculature may result in "lymphedema"<sup>[1]</sup>, which is characterized by retention of lymphatic fluid in the interstitial space, leading to a series of pathological changes, including tissue swelling, chronic inflammation, lipid deposition, and tissue fibrosis<sup>[2]</sup>.

There are two types of lymphedema according to etiology<sup>[3]</sup>. Primary lymphedema comes from developmental or congenital abnormalities of the lymphatic system resulting in dysfunctional lymphatics, which could be symptomatic at birth or more commonly in adolescence. Secondary lymphedema is more common and results from trauma, obstruction, surgery, or infection involving the lymphatic system. Up to 250 million people in developing countries suffer from lymphedema, with the parasitic disease filariasis as the most prevalent cause<sup>[4]</sup>; lymphadenectomy and radiation therapy for cancer treatment are usually the major causes of lymphedema in developed countries.

Chronic lymphedema affects 0.13%-2% of the global population<sup>[5]</sup>. It is estimated that one out of six patients undergoing treatment for a solid tumor will eventually develop lymphedema<sup>[6]</sup>. For patients with breast cancer, 24%-49% of those receiving mastectomy will develop upper extremity lymphedema<sup>[7]</sup>. The persistence of the disease, burden of treatment, and likelihood of progression press heavy medical and socioeconomic burdens onto patients. Therefore, development of effective therapies for lymphedema is of vital importance.

Lymphedema can be treated conservatively, surgically, or by a combination of them<sup>[2]</sup>. Conservative therapies consist of complex decongestive therapy, manual lymphatic drainage, and exercise<sup>[8]</sup>. Surgical therapies include liposuction, wedge resection, Charles procedure (radical excision for limb lymphedema), and lymphatic reconstruction or bypass techniques<sup>[9]</sup>. However, there is a lack of effective and feasible therapies which could radically cure lymphedema<sup>[10]</sup>. Therefore, elucidating the underlying pathophysiological mechanisms of lymphedema holds promise for the

treatment of lymphedema.

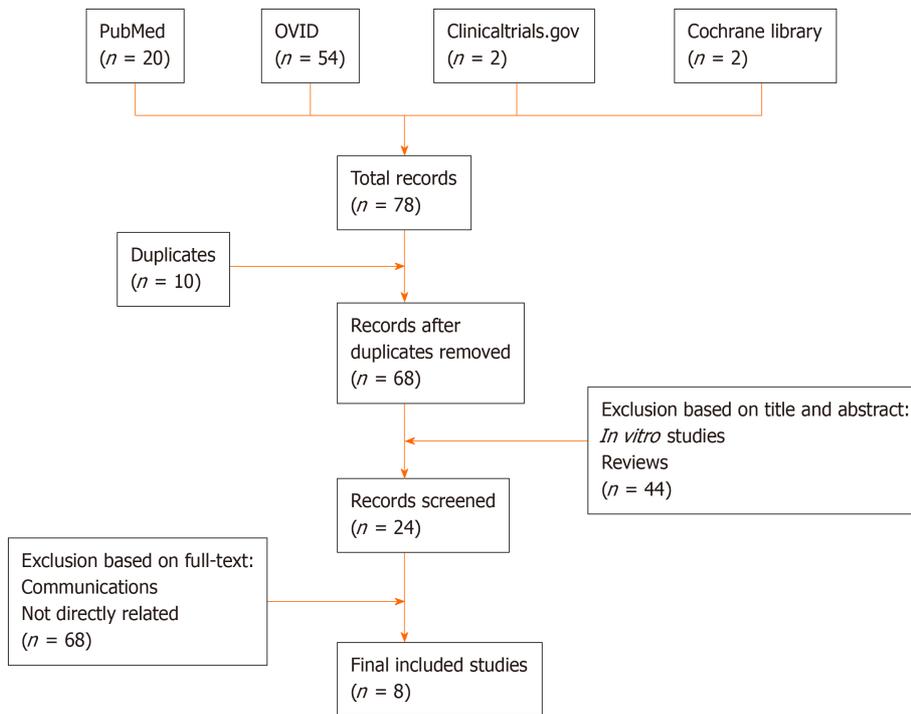
Progenitor or stem cell-based therapies, which treat diseases through regeneration, have represented an alternative treatment method not only for lymphedema but for a wide spectrum of other diseases as well. Due to their abundant resources, easy access, pluripotent capacity, and harboring of few ethical and immunological issues, the adipose-derived stem cells (ADSCs) are considered as one of the most promising seed cell types for regenerative medicine<sup>[11-15]</sup>. In addition, ADSCs exhibit paracrine immunomodulatory and trophic effects in their local microenvironment. Emerging *in vitro* studies have investigated the possible mechanisms and benefit of ADSCs in the treatment of lymphedema, such as their capacity for differentiation into lymphatic endothelial cells (LECs)<sup>[16,17]</sup> and paracrine secretion of cytokines<sup>[18]</sup>, chemokines<sup>[19]</sup> and exosomes<sup>[20]</sup>, thereby promoting angiogenesis and modulating the immune response. Takeda *et al*<sup>[21]</sup> reported that, by secreting lymphangiogenic factors, ADSCs promote proliferation, migration, and tube formation of LECs *in vitro*. Deng *et al*<sup>[22]</sup> demonstrated that overexpression of Prox1 in human ADSCs (*via* lentiviral vectors) induces the differentiation of human ADSCs into stable lymphatic endothelial-like cells *in vitro* and that the differentiated cells form tube-like structures (as shown in tube formation assay). Yen *et al*<sup>[23]</sup> showed that ADSCs promote lymphangiogenesis under stimulation of vascular endothelial growth factor-C (VEGF-C), a key lymphangiogenic factor, or in response to inhibition of TGF- $\beta$ 1; moreover, stimulation of ADSCs with VEGF-C was found to markedly increase cellular proliferation and cellular survival after *in vivo* implantation and to induce the expression of podoplanin, a lymphangiogenic cell marker. Sun *et al*<sup>[19]</sup> reported that interleukin-7 enhanced the differentiation of ADSCs into LECs *via* AKT signaling pathways. Most recently, Saijo *et al*<sup>[24]</sup> revealed that paracrine effects of ADSCs promoted lymphangiogenesis in irradiated LECs. They reported that coculture with ADSCs and the use of ADSC-conditioned medium improved proliferation, migration, and tube formation of nonirradiated LECs. Furthermore, they demonstrated that irradiated ADSCs can exert similar alleviative effects to irradiated human dermal LECs<sup>[24]</sup>.

Collectively, these research findings have suggested that ADSCs might serve as suitable seed cells for lymphatic tissue engineering and secondary lymphedema therapy. The aim of this review is to systematically summarize the application of ADSCs for lymphedema treatment in animal studies and in clinical trials. In addition, the future perspectives of ADSCs in lymphedema therapy are discussed.

## MATERIALS AND METHODS

A systematic search was performed on four databases (PubMed, Clinicaltrials.gov, the evidence-based Cochrane library, and OVID) using the following search string: (“lymphedema” or “lymphoedema” or “lymphangiogenesis”) and (“adipose-derived stem cells” or “adipose-derived stromal cells” or “adipose-derived regenerative cells”). After duplicate removal, all studies were screened based on title and abstract. Furthermore, full-text versions of included studies were read for further evaluation. A manual search was also performed by skimming the references of included studies. The search process is presented in **Figure 1**.

The inclusion criteria were animal studies and clinical trials using adipose-derived cells for treatment of any kind of lymphedema, which had been published no later than November 2019. The exclusion criteria were non-English language, reviews, or *in vitro* studies. For animal studies, data retrieved were year of publication, first author, type of animal models, cell type used (freshly isolated or culture-expanded as well as autologous or allogeneic), cell dosage, cell characterization (cell count/viability, surface marker analysis, *etc.*), means and routes of transplantation (alone or in combination with growth factors, scaffolds, *etc.*), assessment types, and results. For clinical trials, data retrieved were year of publication, country of origin, disease treated, study design (randomized controlled trial, nonrandomized study, or case series/pilot study), number of participants, cell type used (freshly isolated or culture-expanded as well as autologous or allogeneic), cell dosage, cell characterization (cell count/viability, surface marker analysis, *etc.*), means and routes of transplantation (alone or in combination with growth factors, scaffolds, *etc.*), assessment types, and outcomes.



**Figure 1** Search process of articles regarding adipose-derived stem cell-based treatment of lymphedema studied in animal models and clinical trials.

## RESULTS

A total of eight research articles published before November 2019 met the inclusion criteria for this analysis. These included five articles focused on animal studies (Table 1) and three focused on clinical trials (Table 2).

### Animal studies

A total of five animal studies were included in the analysis. Commonly-used animal models were mouse hindlimb or tail model of lymphedema. The surgical procedures were circumferential incision with or without radiation. The number of cells used for injection varied from  $10^4$  to  $10^{10}$  each time. Various treatments were used in combination with cell injection, including controlled-release VEGF-C, platelet-rich plasma (PRP), or vascularized lymph node transfer. Treatment outcomes were evaluated by circumference, dermal edema depth, imaging (lymphangiography and photodynamic dye), and histochemical and immunohistochemical staining (for CD31, LYVE1, and VEGF receptor).

Hwang *et al.*<sup>[25]</sup> established a mouse hindlimb model of lymphedema by electrocauterizing the lymph vessels in the thigh following a circumferential incision. *In vivo* study demonstrated that combination of human (h) ADSCs and VEGF-C hydrogel markedly alleviated dermal edema and increased lymphatic vessel density when compared with results achieved with hADSCs or VEGF-C hydrogel alone at various post-treatment time points (from 3-4 d to 4 wk post-treatment). In addition, the authors demonstrated the existence of hADSCs in all of the implantation sites in the hADSC/VEGF-C group with LECs phenotype. Their results also suggested that, in conjunction with hADSCs, VEGF-C-containing hydrogels could serve as suitable delivery vectors to improve lymphangiogenesis.

Shimizu *et al.*<sup>[26]</sup> reported on the establishment of a mouse tail model of lymphedema. They made a 2 mm-wide circumferential excision on the skin 10 mm distal to the tail base and excluded a 4 mm<sup>2</sup> dermal flap at the ventral side. They indicated that local injection of  $2 \times 10^6$  freshly isolated autologous ADSCs could reduce lymphedema and accelerate lymphangiogenesis at the congestive lymphedema region. The authors also revealed that ADSCs could release VEGF-C to stimulate lymphangiogenesis and recruit bone marrow-derived M2 macrophages to serve as lymphatic endothelial progenitor cells.

Ackermann *et al.*<sup>[27]</sup> assessed the effects of PRP and adipose stem cells on angiogenesis, microcirculation, lymphangiogenesis, microvascular architecture, and

Table 1 Adipose-derived stem cell-based treatment of lymphedema in animal studies

Year	Ref.	Animal	Location and methods	Groups	Cell type used for characterization and number	Implantation methods	Assessment	Results
2011	Hwang <i>et al</i> <sup>[25]</sup>	6-8-wk-old female BALB/c mice	Hindlimb, Circumferential incision and electrocautery	5 groups ( <i>n</i> = 5 for each group): Normal, control, hADSCs, VEGF-C hydrogel, hADSCs/VEGF-C hydrogel	PKH-26-labeled hADSCs N/A	In combination with VEGF-C gelatin hydrogel subcutaneous injection	Dermal edema depth measurement using Vernier calipers  H&E staining  IFC (LYVE-1) for lymphatic vessel intensity	Co-administration of hADSCs and VEGF-C decreased dermal edema depth and increased lymphatic vessel intensity
2012	Shimizu <i>et al</i> <sup>[26]</sup>	7-8-wk-old male C57BL/6 mice	Tail 2 mm-wide circumferential annulus of the skin excision at 10 mm distal to the tail base, excluding a 4 mm <sup>2</sup> dermal flap located at the ventral side	3 groups ( <i>n</i> = 12 for each group): Sham, PBS, and freshly isolated ADRCs	Freshly isolated ADRCs 2 × 10 <sup>6</sup>	Local injection	Tail thickness measurement  IHC analysis (LYVE-1)  IFC staining (LYVE-1, CD11-b, CD163)	Local injection of ADRCs significantly reduced lymphedema ADRC implantation accelerated lymphangiogenesis ADRC implantation enhanced recruitment of M2 macrophages, to serve as lymphatic endothelial progenitor cells
2015	Ackermann <i>et al</i> <sup>[27]</sup>	10-wk-old male C57BL/6 mice	Tail Circumferential 5 mm-wide full thickness excision at a 10 mm distance from the base of the tail	3 groups: Saline, PRP, and ASC	Allogenic 3 passages FACS analyzed (CD31-/CD45-/CD29+/CD90+ cells)	Injection	Angiogenesis (anti-CD31 staining)  Laser Doppler imaging for microcirculation  Lymphangiogenesis (anti-LYVE1 staining)  Corrosion casting for microvascular architecture  Digital planimetry for wound healing	Wounds treated by PRP and ASC healed faster and showed a significantly increased epithelialization  Application of PRP induced a significantly increased lymphangiogenesis, while application of ASC did not induce any significant change, in this regard.
2015	Yoshida <i>et al</i> <sup>[28]</sup>	Male C57BL/6 mice	Right hindlimb, 30-gray x irradiation, surgical lymph node dissection, and 2-mm gap creation	4 groups ( <i>n</i> = 20 for each group with different cell numbers)	Allogenic up to 5 passages 0, 10 <sup>6</sup> , 10 <sup>5</sup> , 10 <sup>4</sup>	Subcutaneous injection	Circumference measurement  Near-infrared video camera for lymphatic flow assessment  IHC for quantitation of lymphatic vessels (LYVE, VEGF-C, VEGFR, and EGFP)  XY chromosome FISH analysis	Number of lymphatic vessels significantly increased at 2 wk  No direct detection of ADSCs involving lymphangiogenesis by EGFP at 2 wk or chromosome FISH at 2 wk and 4 wk

2017	Hayashida <i>et al</i> <sup>[29]</sup>	10-wk-old male C57BL/6J mice	Left hindlimb, 30-Gy X-ray irradiation, surgical lymph node dissection, and 5-mm gap creation	4 groups ( <i>n</i> = 5 for each group): Control, VLNT, ADSCs, VLNT-plus/ADSCs-plus	Allogenic 1-3 passages at 10 <sup>4</sup>	VLNT, subcutaneously	Near-infrared video camera for lymphatic flow assessment  Water-displacement plethysmometer for hind-paw volumetry test  IHC for tissue quantification of lymphatic vessels (LYVE-1, VEGF-C, and VEGF-R3)  B16 mouse melanoma cells for functional analysis of lymphatic vessels and nodes	Increased number of lymphatic vessels  Induced lymphatic flow drainage to the circulatory system
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ADRCs: Adipose-derived regenerative cells; ADSCs: Adipose-derived stem cells; ASC: Adipose stem cells; EGFP: Enhanced green fluorescent protein; FISH: Fluorescent *in situ* hybridization; H&E: Hematoxylin and eosin; hADSCs: Human adipose-derived stem cells; IFC: Immunofluorescence; IHC: Immunohistochemistry; N/A: Not applicable; PBS: Phosphate-buffered saline; VEGF-C: Vascular endothelial growth factor-C; VEGF-R3: Vascular endothelial growth factor-receptor 3; VLNT: Vascularized lymph node transfer.

wound healing in a mouse tail lymphedema model. They found that treatment with PRP and adipose stem cells could accelerate wound healing and increase epithelialization. PRP application induced a remarkably improved lymphangiogenesis. Ultimately, the authors drew the conclusion that PRP and adipose stem cells can affect lymphangiogenesis and lymphedema development.

Yoshida *et al*<sup>[28]</sup> reported on the establishment of a mouse right hindlimb secondary lymphedema model, using 30 Gy X-ray irradiation 7 d before surgery to create a circumferential incision and a gap of approximately 2 mm, left open. Circumferential measurement, lymphatic flow assessment, and quantification of lymphatic vessels demonstrated that at 14 d post-treatment of local injection with 10<sup>6</sup> ADSCs, 10<sup>5</sup> ADSCs, or 10<sup>4</sup> ADSCs, the numbers of lymphatic vessels were significantly increased in the transplanted groups; the authors concluded that in secondary lymphedema, ADSCs could increase collecting vessels and reconstruct the lymphatic vascular network. A more recent study from the same research group<sup>[29]</sup> demonstrated that local implantation of 10<sup>4</sup> ADSCs in combination with vascularized lymph node transfer decreased tissue volume, increased lymphatic vessels density, and improved the lymphatic function in a slightly different mouse hindlimb model (left *vs* right hindlimb, 5 mm- *vs* 2 mm-wide gap, left open).

### Clinical trials

A total of three clinical trials were included in the analysis. All these studies were conducted by the same research group in Denmark<sup>[25-27]</sup>, focusing on upper limb and breast cancer-related lymphedema (BCRL), using freshly isolated autologous ADSCs

Table 2 Adipose-derived stem cell treatment of lymphedema in clinical trials

Year	First author	Study type	Patient number, test/control	Edema location	Cell type	Cell number	Injection method, location/depth	Follow-up inmo assessment	Results
2016	Toyserkani <i>et al</i> <sup>[30]</sup>	Pilot study	1/0	Upper limb	Freshly isolated autologous ADSCs plus fat graft	4.07 × 10 <sup>7</sup> plus 10 mL lipoaspirate	Axillary region (8 points)	4 mo <i>In vitro</i> cell characterization (cell count, viability, and surface marker)	Great reduction in symptoms of arm heaviness and tension, reduction in need for compression therapy
								Circumference measurements	Volume reduction in affected arm
								Dual-energy X-ray absorptiometry scans Adverse events	No postoperative complications or adverse events
2017	Toyserkani <i>et al</i> <sup>[31]</sup>	Pilot study	10/0	Upper limb	Freshly isolated autologous ADSCs plus fat graft	5 × 10 <sup>7</sup> plus 30 mL lipoaspirate	Axilla (8 points)	6 mo <i>In vitro</i> cell characterization (cell count, viability, and surface marker)	A small volume reduction but not significant
								Circumference measurements	Patient-reported outcomes improved significantly over time
								Dual-energy X-ray absorptiometry scans	Half of the patients reduced their use of conservative management
2019	Toyserkani <i>et al</i> <sup>[32]</sup>	Pilot study	10/0	Upper limb	Freshly isolated autologous ADSCs plus fat graft	5 × 10 <sup>7</sup> plus 30 mL lipoaspirate	Axilla (8 points)	12 mo <i>In vitro</i> cell characterization (cell count, viability, and surface marker)	No significant change in volume
								Circumference measurements	Patient-reported outcomes improved significantly over time
								Dual-energy X-ray absorptiometry scans	Five patients reduced their use of conservative management
								Patient-reported outcome and safety questionnaire assessment	Quantitative lymphoscintigraphy showed no improvement on the lymphedema-affected arms
								Lymphoscintigraphy changes	ADRCs were well-tolerated and only minor transient adverse events related to liposuction were noted

ADRCs: Adipose-derived regenerative cells; ADSCs: Adipose-derived stem cells.

with fat grafting. The follow-up period ranged from 4 mo to 1 year.

In 2016, Toyserkani *et al*<sup>[30]</sup> reported a pilot study using ADSC-assisted lipotransfer to treat lymphedema. A 48-year-old female patient developed BCRL after lymphadenectomy and radiation therapy. A total of 4.07 × 10<sup>7</sup> freshly isolated autologous ADSCs were administered, along with 10 mL of lipoaspirate (for fat-grafting), to the axillary region. At 4 mo post-treatment, the authors noted that the daily symptoms of arm heaviness and tension were greatly relieved, the needs for compression therapy were reduced, and the volume of the affected arm was decreased without postoperative complications or adverse events.

Furthermore, the authors had also performed a larger study to validate the feasibility and safety of this procedure in 2007<sup>[31]</sup>, which was registered at

Clinicaltrials.gov under the identifier NCT02592213 at phase 2 stage. In this pilot study, ten BCRL patients were included. Combined with a scar-releasing fat graft (about 30 mL) procedure, approximately  $5 \times 10^7$  freshly isolated adipose-derived regenerative cells (ADRCs) were injected into the axillary region. During a 6-mo follow-up period, there was a small but not significant volume reduction. Five of the patients showed a reduced need for conservative treatment, and patient-reported follow-ups improved significantly over time. Slight, temporary adverse events were observed, but were more likely caused by liposuction procedures rather than ADRC injection. Ultimately, the ADRCs were deemed as well-tolerated.

In 2019, the results of lymphoscintigraphic evaluation with 1-year follow-up were reported<sup>[32]</sup>. Consistent with the results of the 6-mo follow-up, ADRC injection improved lymphedema, as revealed by patient-reported outcomes without serious adverse events. However, there was no improvement in lymphoscintigraphic evaluation and no change in arm volume after the ADRC treatment. Now, this research group is recruiting patients for a randomized phase 3 trial, which is registered at Clinicaltrials.gov under the identifier NCT03776721. This study started December 17, 2018 and the estimated study completion date is September 1, 2021, designed to recruit 80 participants with a parallel assignment to evaluate the efficacy and safety of implantation of freshly isolated adipose-derived stromal cells in combination with fat grafting at the affected axillary region.

## DISCUSSION

Lymphedema, characterized by tissue swelling, lipid deposition, and fibrosis due to excess accumulation of interstitial fluid and inadequate lymphatic drainage, affects 0.13%-2% of the global population<sup>[5]</sup> and remains a chronic, debilitating and incurable disease. Stem cell-based regenerative medicine has shown great promise for refractory diseases, such as inflammatory bowel diseases<sup>[33]</sup>, heart failure<sup>[34]</sup>, osteoarthritis<sup>[35]</sup>, rheumatoid arthritis<sup>[36]</sup>, and graft-versus-host disease<sup>[37]</sup>. With the properties of self-renewal, multipotential differentiation, paracrine, immunomodulatory, and trophic effects, and low immunogenicity alongside their practical advantages, ADSCs have become one of the most promising candidates for regenerative medicine.

ADSCs are isolated from the aqueous fraction – known as the stromal vascular fraction (SVF) – by means of enzymatic digestion of lipoaspirate (liposuction product)<sup>[38,39]</sup>. As the major source of ADSCs, SVF is a heterogeneous cell group composed of ADSCs, endothelial precursor cells, endothelial cells, macrophages, smooth muscle cells, lymphocytes, pericytes, and pre-adipocytes derived from fat tissue. Recent advances have shown the role and efficacy of SVF and ADSCs in improvement of tissue regeneration, especially in plastic reconstruction<sup>[40]</sup>, such as breast reconstruction<sup>[41,42]</sup>, wound healing<sup>[43,44]</sup>, scars<sup>[45,46]</sup>, and soft tissue defects<sup>[47]</sup>. The SVF is more easily obtained, regardless of cell separation and culture conditions. Therefore, therapeutic cellular products are obtained immediately with minimal contact with reagents, making it not only technically easier but also relatively safer. At the same time, the unique heterogeneous cell components of SVF may achieve better treatment results in comparative animal studies. It is worth noting that SVF might be suitable for autologous therapy only, due to the existence of various cell types that might cause immunological rejection<sup>[48]</sup>, whereas ADSCs are useful in both allogeneic therapy and autologous therapy.

As mentioned in the first part of this review, emerging *in vitro* studies have already definitively demonstrated the advantage of ADSCs in lymphangiogenesis and treatment of lymphedema. All five animal studies included in this systematic review were performed on mouse models and the ADSCs were injected immediately or shortly after lymphedema induction. These studies examined the effect of ADSCs on acute lymphedema and exhibited improvement at 4-6 wk. However, the anatomy, physiology, and healing capacity are quite different between mice and human beings, bringing up the need for larger animal models in order to simulate chronic lymphedema in human beings more accurately. Further preclinical studies with better animal models are needed to determine whether ADSC-based therapies could fulfil expectations and be extrapolated to clinical use in patients. As is commonly known, to observe lymphatics in mice, it is usually necessary to visualize the blue dye-stained lymphatic vessels in dissected tissues or tissue sectioning for immunohistological staining for the lymphatic markers, such as VEGFR-3, PROX1, and LYVE1, to quantitatively identify lymphatic vessel intensity and lymphangiogenesis. Advances in near-infrared fluoroscopy lymphatic imaging<sup>[49]</sup>, magnetic resonance imaging agents

based on nanotechnology, and gene reporter technologies have paved roads for depicting functions of lymphatic vasculature. Though not all lymphatic imaging methods are suitable for both clinical and preclinical trials, their effective combination will provide new tools for lymphedema translational medicine<sup>[50]</sup>.

Therapy of lymphedema has benefitted substantially from the most recent advances in lymphatic vessel engineering and regenerative medicine, including cell-seeded scaffolds for vessel reconstruction, implantation of stem cells, prolymphangiogenic growth factors, or a combination of these technologies. As mentioned above, when implanted into the injury site in a lymphedema mouse model, the gelatin hydrogel containing controlled-release VEGF-C could encapsulate hADSCs, increase vessel density, and improve dermal edema, leading to efficient application in lymphatic vessel regeneration<sup>[25]</sup>. It has been reported that SVFs and ADSCs could improve wound healing when used alone or in combination with PRP and hyaluronic acid, specifically in healing of lower-extremity soft- and hard-tissue wounds<sup>[43]</sup> and in severe hidradenitis suppurativa wounds<sup>[47]</sup>. Many other studies confirmed that SVFs and ADSCs can improve wound healing when used alone or in combination with PRP and fat graft<sup>[41,45,51,52]</sup>. Considering the similar biological processes and biomolecular pathways shared between wound healing and lymphedema, such as inflammation and angiogenesis, the efforts towards establishing ADSCs-based therapy for lymphedema will benefit from these studies. Certainly, the research efforts towards development of cell isolation and expansion methods and of three-dimensional scaffolds<sup>[53]</sup>, nanoparticles, and targeted delivery will help to optimize and maximize the efficacy of ADSC-assisted therapy. Standardized platforms with minimized manipulations and maximized efficacy will facilitate both up-scaling and the ease of clinical translation.

Over the past few years, concerns regarding the safety of stem cell application have also been raised. Indeed, Toyserkani *et al*<sup>[54]</sup> performed a systematic review, including over 1400 patients who received ADSC treatment and were followed for 4 wk to 3 years, in order to assess the safety of ADSC therapy, concentrating on the risks of thromboembolical, immunological, and oncological safety concerns. They reported that the observed adverse outcomes were relevant to liposuction, injuries from implantation, or the underlying condition, rather than the ADSC therapy itself. Although the ADSC therapy has shown a favorable safety performance, more reliable and rigorous safety assessment approaches are still encouraged for further study and clinical practice.

In conclusion, the results of *in vitro* studies, animal models, and clinical trials characterize ADSC-based treatment as a promising option and one that can be used within biologically rational and controllable environments for the treatment of lymphedema. However, further investigations in larger animal models and larger-scale, multicenter randomized clinical trials with more reliable and rigorous safety assessments are needed to develop more effective and durable therapeutic strategies.

## ARTICLE HIGHLIGHTS

### Research background

Lymphedema is a chronic, debilitating and incurable disease that affects 0.13%-2% of the global population. Emerging evidence indicates that adipose-derived stem cells (ADSCs) might serve as suitable seed cells for lymphatic tissue engineering and lymphedema therapy. Here, we appraise the *in vivo* evidence for the application of ADSCs for lymphedema treatments.

### Research motivation

Emerging research findings have suggested that ADSCs might serve as suitable seed cells for tissue engineering of lymphatic vessels *in vitro* and potentially in the treatment of secondary lymphedema *in vivo*. It is critical that we systematically summarize the application of ADSCs for lymphedema treatments in animal studies and in clinical trials and discuss the future perspectives.

### Research objectives

The main objectives of this review are to systematically summarize the application of ADSCs for lymphedema treatments as shown in animal studies and clinical trials. In addition, the future perspectives of ADSCs in lymphedema therapy are discussed.

### Research methods

A systematic search was performed on four databases – PubMed, Clinicaltrials.gov, the evidence-based Cochrane library, and OVID – using the following search string: (“lymphedema” or “lymphoedema” or “lymphangiogenesis”) and (“adipose-derived stem cells” or “adipose-derived stromal cells” or “adipose-derived regenerative cells”). A manual search was performed by skimming the references of relevant studies. Animal studies and clinical trials using adipose-derived cells for the treatment of any kind of lymphedema were included.

### Research results

A total of eight research articles published before November 2019 were included for this analysis. Five articles focused on animal studies and another three focused on clinical trials. ADSC transplantation therapy was demonstrated to be effective against lymphedema in all studies. The animal studies found that coadministration of ADSCs and controlled-release vascular endothelial growth factor-C or platelet-rich plasma could improve the effectiveness of ADSC therapy. Three sequential clinical trials were conducted on breast cancer-related lymphedema patients, and all showed favorable results.

### Research conclusions

The results of *in vitro* studies, animal models, and clinical trials characterize ADSC-based treatment as a promising option and one that can be used within biologically rational and controllable environments for the treatment of lymphedema.

### Research perspectives

Further preclinical studies in larger animal models and large-scale, multicenter randomized controlled clinical trials with more reliable and rigorous safety assessments are needed to develop more effective and durable therapeutic strategies. Advances in lymphatic imaging methods will provide opportunities for lymphedema translational medicine as well.

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