



## Treatment of Peripheral Lymphedema

Ningfei Liu\*

Department of Plastic and Reconstructive Surgery, Shanghai Jiao Tong University School of Medicine, China

### Abstract

Few breakthroughs have been made in the treatment of lymphedema because of a lack of information about the embryonic development and physiological function of the lymphatic system, pathophysiology and prognosis of lymphedema, and a lack of sophisticated and high-resolution imaging methods. The indications and evidence for the safety and efficacy of current surgical treatments are not clear-cut. The present mainstream treatment for lymphedema is complex decongestive therapy. Recent advances in multimodal lymphatic imaging have improved the accuracy of diagnosis of lymphatic disorders, necessitating new requirements and expectations for the treatment of peripheral lymphedema, the ultimate goal being to achieve individually tailored treatment. Treatment of peripheral lymphedema must be based on the following principles: a) Distinguishing primary from secondary lymphedema. The function and structure of the lymphatic system differ substantially between these two conditions. Lymphatic vessel regeneration and self-repair in primary lymphedema require further investigation. b) Paying particular attention to pathological changes and their evolution in lymphatic vessels in the affected area, such pathological changes (sclerosis) in lymphatic vessels (and maybe also in lymph nodes) possibly being irreversible. c) Including addressing pathological changes in lymphedema-affected tissues (including irreversible changes such as chronic inflammatory reactions, fibrosis, and fat deposition) among the treatment targets. Decreasing the expression of inflammatory cytokines in tissues and blocking their functions at the molecular level may provide a new insight into and approach to treating lymphedema.

**Keywords:** Lymphedema; Complex decongestive therapy; Microlymphatic surgery; Lymphatic imaging

### Introduction

Peripheral lymphedema, the commonest form of lymphatic disorder, occurs mainly in the extremities and rarely in the external genital organs and face. Lymphostasis caused by congenital or unexplained dysplasia of the lymphatic system is called primary lymphedema, whereas the obstructive lymphostasis caused by the absence or obstruction of lymph vessels and/or lymph nodes following surgery, trauma, infection, and/or radiotherapy is known as secondary lymphedema. Although the lymphatic systems were discovered at almost the same time, knowledge about the lymphatic system lags far behind that about the blood system. In 2016, Science listed the discovery of lymphatic vessels in the brains of mice as one of the top ten scientific discoveries [1]. Considering that, Foeldi, a famous German lymphologist, described lymphatic vessels in the brain in the early 1990s [2,3]; the rediscovery of cerebral lymphatic vessels in 2016 indicates that the lymphatic system was generally poorly understood. This limited knowledge about the embryonic development and physiological function of the lymphatic system and the associated poor understanding of the pathophysiology of lymphatic disorders and the prognosis of lymphedema is responsible for the paucity of breakthroughs in the treatment of lymphedema.

Early-stage peripheral lymphedema is currently mainly treated surgically. However, surgeries (e.g., Charles procedure) that aim to reduce the size of the affected limb can cause considerable trauma and thick and unstable scars leading to severe complications, including lymphatic leakage, chronic ulceration, and even malignant transformation. In addition, they do not restore impaired lymphatic return. No published studies have described the long-term effectiveness of dissociation and pedicled transplantation of the greater omentum to the axillary or inguinal region [4]. The greater omentum should not be regarded as a tissue because it is an organ with unique functions [5] and should therefore not be used rashly as a graft.

Liposuction is designed to reduce the size of the affected limb by removing as much as possible of the subcutaneous fat and fibrous tissue. This procedure preserves the integrity of the skin. Unlike individuals undergoing cosmetic liposuction, those with lymphedema should be under go long-

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#### \*Correspondence:

Ningfei Liu, Department of Plastic and Reconstructive Surgery, Shanghai Jiao Tong University School of Medicine, China, Tel: +86-21-23271699x5734;

Fax: +86-21-53078128;

E-mail: liuningfei@126.com

Received Date: 24 Oct 2018

Accepted Date: 20 Nov 2018

Published Date: 23 Nov 2018

#### Citation:

Liu N. Treatment of Peripheral Lymphedema. Clin Surg. 2018; 3: 2228.

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term compression therapy after surgery to avoid rebound edema because lymphatic vessels and lymph backflow of the affected limb cannot be reconstructed or restored.

In the 1970s and 1980s, microlymphatic bypasses such as lymphatic venous anastomosis were performed to treat various forms of primary and secondary lymphedema, including middle and advanced stage lymphedema. In recent years, the indications for such procedures have become more stringent. Although the long-term patency rate of lymphatic venous anastomosis has not been well studied, this procedure remains one of the most commonly performed surgical treatments.

Both lymphatic vessel and lymph node have been transplanted to restore lymph circulation and autologous lymphatic vessel transplants have remained patent for more than 10 years [4]. Lymph nodes with their blood supply have been transplanted to prevent and treat limb lymphedema; however, the long-term outcomes of this procedure have yet to be determined. Whereas imaging examinations have confirmed the presence of blood flow to the transplanted lymph nodes, lymphatic reflux through these transplanted lymph nodes has rarely been reported.

Notably, the indications and evidence for, and safety and efficacy of, currently performed surgical treatments are not clear-cut because of a lack of means of sophisticated and high-resolution imaging.

The most well-known non-surgical treatment for lymphedema in China is far-infrared hyperthermia, also known as heating and bandaging treatment, which was described by Dr. Zhang Disheng in the 1960s and 1970s and has been performed in Shanghai Ninth People's Hospital since then [6]. This technique uses a specially designed far-infrared therapeutic apparatus with elastic bandaging and remarkably reduces the incidences of erysipelas and other skin infections in association with alleviating edema [7,8].

Meanwhile, Complete Decongestive Therapy (CDT), which is based on manual lymphatic drainage, has been gradually popularized worldwide to become the most widely used and effective treatment for peripheral lymphedema [5]. In 2007, Shanghai Ninth People's Hospital became the first Chinese center to apply this procedure [9] since which many hospitals in China has introduced CDT. Peripheral lymphedema can typically be treated by non-operative methods such as CDT because it usually progresses slowly and is incurable, thus requiring lifelong care like other chronic diseases. Non-surgical treatment such as CDT is helpful for slowing down the progression of peripheral lymphedema, minimizing the incidence and severity of complications, and improving the quality of life. Although CDT does not cure lymphedema, it has a wide range of indications and is safe, effective, and robust, warranting further promotion.

Ideally, treatments should target the causes of and pathological changes in a disease; these principles apply in the treatment of peripheral lymphedema. In recent years, new lymphatic imaging techniques have improved the diagnosis of lymphatic disorders [4]. MR lymphangiography has high resolution, enabling real-time dynamic observation of lymph flow; thus, it can be used to assess the morphology and function of peripheral lymphatic malformations simultaneously. Indocyanine green fluorescence (ICG) lymphography has lower resolution but can easily be used for real-time lymphography of any part of the body's surface. This is also a reliable means of examining lymphatic function. Single-Photon Emission Computed Tomography (SPEC CT) lymphography, a novel

technique based on radionuclide lymphography, enables accurate observation of the deep lymphatic system and is thus helpful in identifying and locating lesions in deep lymph nodes and lymphatic vessels. Therefore, multimodal lymphatic imaging can increase the accuracy of diagnosis of disorders of the peripheral lymphatic system, allowing clinicians to identify morphological and functional abnormalities in detail before treatment and to classify or categorize the pathological types. In fact, over the past three decades there have been dramatic improvements in the capability to diagnose peripheral lymphatic disorders; thus, new requirements and expectations have been proposed for the treatment of peripheral lymphedema, with tailored treatment as the ultimate goal. The following issues regarding treatment of peripheral lymphedema therefore need to be addressed.

### **Distinguishing between primary and secondary lymphedema**

Primary peripheral lymphedema is generally confined to a single limb and rarely seen in more than two limbs. Lymphedema of the extremities can be caused by a rare and complex combination of syndromes such as lymphedema–distichiasis syndrome and Hennekam syndrome. Chylous reflux syndrome accompanied by intestinal lymphatic malformations is also a rare such combination.

Morphologically, lymphatic system malformations in primary lymphedema can be roughly divided into four categories: a) lymph node affected only, that is, regional (groin or axillary) lymph node disorder; b) lymph vessel affected only, that is, evident pathological changes (hyperplasia, hypoplasia, aplasia) of lymph vessels; c) both lymph nodes and lymphatic vessels affected; [10] and d) lymphatic vessel dysfunction, in which the lymphatic vessels are partly visible or completely undetectable radio graphically but histological examination reveals that they are present [11].

Thus, causes of primary lymphedema are complex and can include a variety of pathological factors. Solid knowledge and proper classification of lymphedema before instituting treatment facilitates more individualized treatment and avoids or reduces therapeutic blindness. For example, limb lymphedema caused by simple lymphadenopathy may be treated by transplanting autologous healthy lymph nodes, and obvious structural abnormalities (e.g. tortuous dilatation, insufficient valvular closure, and scarcity or insufficient contrast visualization) of the lymphatic vessels in the affected limbs indicate that the lymphatic vessels themselves have varying degrees of dysfunction. Use of such lymphatic vessels for diversion surgeries such as lymphatic–venous anastomosis and superficial–deep lymphatic anastomosis prejudices improvement in lymphatic circulation. Therefore, preoperative assessment of lymphatic vessel function is essential.

Notably, many patients with primary lymphedema also have disorders of the venous system (e.g., deep venous valvular insufficiency, varicose veins) in the affected limbs, making them unsuitable for lymphatic diversion. Because primary lymphedema usually affects the entire limb, it is not practicable to reconstruct or "regenerate" the lymphatic circulation of the affected limb by removing the diseased lymphatic vessels and replacing them with lymphatic vessels from other sources. Lymphatic vessel regeneration and self-repair in primary lymphedema are as yet inadequately explored issues that require further investigation.

Secondary lymphedema refers to obstruction of the lymphatic circulation caused by surgery, trauma, infection, radiation or other

factors or a combination thereof in an otherwise healthy lymphatic system. The obstructed lymphatic vessels may become dilated, tortuous, or even rupture [12]. Injured lymphatic vessels are capable of self-repair or regeneration [12]. Secondary lymphedema following radical axillary lymphadenectomy for breast cancer, lymphadenectomy for pelvic malignancies in women, or radiotherapy or a combination thereof results from failure to regenerate lymphatic vessels (nodes) after damage by local scarring and tissue fibrosis or removal. Fibrous or scar tissue in the recipient area can prejudice connection and recanalization of grafted lymphatic vessels; therefore, the effectiveness of treating limb lymphedema by free flap (with lymph nodes) transplantation depends largely on whether the scar tissue in the recipient area has been completely removed. Repair and reconstruction procedures should be performed as early as possible in patients with secondary lymphatic damage to maximize their effectiveness and its duration. Lymphatic-venous shunts can reportedly remain patent for as long as 20 years [4]. Lymph node transplantation and lymphatic-venous anastomosis in radical mastectomy for breast cancer as prophylactic treatments have rarely been reported, and their effectiveness remains to be explored in long-term controlled observational studies.

### Pathological changes in lymphatic vessels and their evolution

Lymphedema is a progressive pathological process during which lymphatic vessels undergo progressive pathological changes. In the early stage of the disease, these changes include increased internal pressure, dilatation of the vascular lumen, rupture of the vascular wall, and incomplete valve closure. As the disease progresses, the tunica media of the lymphatic vessel wall becomes thicker, mainly because of smooth muscle wrapping, wall sclerosis, and weakening of contractile function [13]. Not only the collecting lymphatic vessels, but also the lymphatic capillaries change, the monolayer lymphatic endothelial cells in the latter being encapsulated by smooth muscle and thickened. Lymphangiosclerosis can be seen in the skin of patients with either primary or secondary lymphedema, suggesting it is common to all types of lymphedema [14]. Sclerosis of lymphatic capillaries may affect closure of endothelial cells, resulting in bidirectional flow of tissue fluid in lymphatic vessels and tissue spaces; this may be the pathological basis of the dermal backflow detected by medical imaging. Given that lymphatic vessel sclerosis may be irreversible, early treatment optimizes the likelihood of good outcomes.

### Pathological changes in lymphedema constitute therapeutic targets

Pathological changes in lymphedematous tissue include lymphatic retention, chronic inflammatory, tissue fibrosis, and fat deposition. These changes are generally irreversible and worsen over time. The disease mainly manifests as edema in its early stage, whereas in later stages fat deposition becomes more obvious. Chronic inflammation and tissue fibrosis characterized by monocyte exudation in the tissue and collagen deposition persist throughout the course of the disease. The main treatment goals are to remove edema in the early stage and eliminate adipose or fibrous tissue or both in advanced stages; furthermore, anti-inflammatory and anti-fibrotic therapies should be prescribed throughout the course of the disease. There is no medical means of eliminating edema in patients with lymphedema. If surgical treatment to drain lymphatic fluid that has stagnated in the tissues is impractical or contraindicated, the following physical therapies can be considered: a) manual lymphatic drainage aimed at guiding

lymph to pass through lymphatic-lymphatic anastomoses and lymphatic-venous communicating branches; and b) compression therapy to reduce exudation of lymph from capillaries and increase lymphatic return via lymphatic vessels and veins in the affected limbs. Compression therapy can also break down existing fibrous tissue and inhibit its formation. The mechanism of tissue fibrosis following lymphedema differs from that of visceral (liver and lung) fibrosis and also from that of skin scarring/fibrosis. Although the exact mechanisms governing tissue fibrosis and its progression remain unclear, it has been shown that inflammatory cells and the inflammatory cytokines secreted by these cells are closely associated with collagen proliferation and fibro lipid deposition in tissue affected by chronic lymphedema [15]. Decreasing the expression of inflammatory cytokines in such tissue and blocking their functions at the molecular level may be a new way of treating lymphedema. There are no ideal strategies for managing accumulation of microbes and metabolites in diseased tissues; antibiotics are the main means of treating and preventing inflammation.

In recent years, several mutated genes related to lymphatic malformation and lymphedema have been identified. Primary lymphedema is probably caused by mutations in multiple genes rather than by a mutation in a single gene [11]. Studies have also shown that genetic variations increase the risk of developing secondary lymphedema after lymphadenectomy [4]. With further investigation of genes associated with the pathogenesis of lymphedema, gene screening is expected to become a diagnostic tool in both primary and secondary lymphedema. Together with multi-modality imaging, it is expected to gradually enable development of targeted therapy for different genes and gene groups.

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