Management of lymphoedema

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Review

Management of lymphoedema

Ahmet Yüksel[1], Orçun Gürbüz[2], Yusuf Velioğlu[3], Gencehan Kumtepe[2], and Sefa Şenol[4]

[1] Department of Cardiovascular Surgery, Bingol State Hospital, Bingol, Turkey
[2] Department of Cardiovascular Surgery, Balikesir University Faculty of Medicine, Balıkesir, Turkey
[3] Department of Cardiovascular Surgery, Abant Izzet Baysal University Faculty of Medicine, Bolu, Turkey
[4] Department of Cardiovascular Surgery, Elazig Education and Research Hospital, Elazig, Turkey

Summary: Lymphoedema is a common and progressive disease which causes deterioration of the quality of life of patients. It is divided into two groups: primary and secondary lymphoedema. Nowadays, the majority of patients with lymphoedema are associated with a malignancy or its treatment modalities, such as cancer surgery and radiation therapy. Accurate diagnosis and effective treatment are crucial for alleviating the symptoms, preventing progression and reducing the potential risks of lymphoedema. This report provides an overview of the management of lymphoedema.

Key words: Lymphoedema treatment, cancer, radiation, chronic venous insufficiency, lymphatic surgery, compression therapy

Introduction

Lymphoedema is a common, chronic, progressive and often debilitating disease caused by the accumulation of protein-rich fluid in the interstitial spaces. Lymph stasis induces an inflammatory reaction that leads to the proliferation of adipose tissue and to fibrosis, resulting in mild to severe, and permanent swelling of the affected body parts [1, 2]. Lymphoedema most frequently affects the extremities, but may occur in the head, neck, torso, abdomen, and genitalia. Lymphoedema impairs quality of life through an increase in skin turgor, loss of dexterity, heaviness in the affected limbs, pain, discomfort, recurrent infections, and psychological complications [3, 4].

Lymphoedema is related to congenital lymphatic abnormalities (primary forms) or acquired (secondary forms) lesions of the lymphatic system. Primary lymphoedema is a lymphoedema without any cause to explain lymphatic impairment, due to abnormal lymphangiogenesis *in utero*. It is often associated with a mutation of a gene involved in lymphangiogenesis (FOX C2, VEGFR 3, SOX18, PROX 1, etc.). Primary lymphoedema has been classified into 3 groups depending on the age of onset of clinical manifestations: Congenital (before the age of 2 years), praecox (between the ages of 2 and 35 years), and tarda (after the age of 35 years). The most common form of primary lymphoedema is praecox. Secondary lymphoedema is the result of an obstruction or disruption of the lymphatic system, which can occur as a consequence of malignancy, trauma, surgery, infection, inflammation, or radiation therapy; and the resulting mechanical insufficiency can lead to the accumulation of fluid in the interstitial spaces. The most common causes of secondary lymphoedema in the Western world are surgery and radiation therapy, which are used to treat cancer. Overall, secondary lymphoedema is much more common than primary lymphoedema [5–7]. Lymphoedema has been defined as one of the most significant survivorship issues after the surgical treatment of breast cancer, and in this population has been documented to have significant physical, functional, economic consequences, and impairment of quality of life [3,8,9]. The incidence of secondary lymphoedema reported in different studies varies widely as a result of the diversity in cancer treatment and measurement methods [10]. For example, the incidence of lymphoedema after surgical treatment of breast cancer varies widely between 6 % and 63 %, depending on the population studied, measurement criteria used, and reported length of follow-up [8-10]. Apart from breast cancer, secondary lymphoedema also has been reported as a consequence of treatment for several solid tumours, including gynaecological, genitourinary, head/neck malignancies, melanoma, and sarcoma [11]. A common feature among these malignancies is the pattern of disease progression, with the development of regional lymphatic metastases often occurring before distant metastatic disease. The oncologic principles for treating regional lymph node metastases often include the surgical dissection and complete resection of the involved lymph nodes (i.e., axillary, inguinal, pelvic).

The International Society of Lymphology staging which defines four stages of lymphoedema is the most commonly used system. Stage 0 or latent/subclinic (no noticeable swelling despite impaired lymph transport), stage 1 (visible swelling that resolves with elevation), stage 2 (visible swelling that does not resolve with elevation), and stage 3 or lymphostatic elephantiasis (trophic skin changes, deposition of fat and fibrosis, and warty overgrowths). When only one limb is affected within each stage, the level of severity is described by comparing the volume of the affected limb to that of the healthy limb. Volume difference up to 20 % is considered minimal, between 20 % and 40 % is considered moderate, and above 40 % is considered severe lymphoedema [12].

Clinical evaluation and diagnosis

An accurate diagnosis of lymphoedema is essential for appropriate treatment. In most patients, the diagnosis of lymphoedema can be readily established from a detailed history including family history and physical examination. The patients are often admitted with signs and symptoms of lymphoedema including limb swelling, non-pitting oedema, skin changes such as hyperkeratosis, dermatitis, red skin discoloration, ulceration, lymph vesicles, peau d'orange or nail abnormalities. Stemmer sign (squaring of the toes) or puffiness of the forefoot (buffalo hump) can also be present in most patients. The presence of venous insufficiency is a significant contributor of lymphoedema. Venous reflux, elevated venous pressure and venous stasis affect the lymphatic flow and drainage, and lead lymphostatis. Therefore, the proper treatment of venous sufficiency is essential in the treatment of lymphoedema. In other patients with confounding conditions such as morbid obesity, lipodystrophy, endocrine dysfunction, occult trauma, and repeated infections, this may complicate the clinical view. Furthermore, in considering the basis of unilateral extremity lymphoedema, especially in adults, an occult visceral tumour obstructing or invading more proximal lymphatics needs to be considered. For these reasons, a thorough medical evaluation is indispensable before embarking on lymphoedema treatment. Comorbid diseases such as congestive heart failure, hypertension and cerebrovascular diseases may also influence the therapeutic approach [5, 12, 13].

Patients may develop chronic pain, anxiety, or depression as well as difficulties with range of motion, activities of daily living, gait, stress on their joints, and fitting into normal clothing [14, 15]. Additionally, lymphoedema swelling more than doubles the risk of developing cellulitis in the affected extremity. Such cellulitis typically progresses quickly and is much more severe in patients with lymphoedema than patients without lymphoedema, and the management often requires hospitalisation for intravenous antibiotics, with some patients requiring long-term, continual low-dose antibiotic prophylaxis. In rare cases, chronic lymphoedema is associated with increased incidence of malignancies such as lymphoma, Kaposi sarcoma, and lymphangiosarcoma (Stewart-Treves syndrome) [16, 17].

The preferred method for the diagnosis of lymphoedema is radionuclide lymphoscintigraphy. It is performed by intradermal or subcutaneous injection of technecium-labelled sulphur colloid or technecium-labelled human serum albumin into the interdigital spaces of the dorsal parts of the foot or hand. Then, after its resorption and patient exercise, a gamma camera records a movement of the lymph [18]. It is minimally invasive and enables making both qualitative and quantitative analyses. Movement of the colloid from the injection site, transition time to the knee, groins, or axilla, absence or presence of the major lymphatic collectors, the number and size of the vessels and nodes, the presence of collateral and reflux, and the symmetric activity with the opposite side are used for interpretation. Lymphoscintigraphy is useful for identifying the specific lymphatic abnormality and has largely replaced conventional oil contrast lymphangiography for visualising the lymphatic network. It can be readily repeated with minimal risk and permits identification of lymphatic dysfunction, lymph nodes, dermal backflow, and semi-quantitative data on radiotracer lymph transport [13]. Contrast lymphangiography comprises direct cannulation of a lymphatic vessel on the dorsum of the foot or hand (under magnification). An oil-based contrast agent is then injected through this vessel and serial plain radiographs of the limb are taken, allowing the lymphatics to be precisely delineated. Due to the potential risk of damage to lymphatic vessels, it can worsen lymphoedema and, thus, is not commonly used [19]. Computed tomography may be helpful in the differential diagnosis of swollen limbs. Computed tomography analysis is based on skin thickening, subcutaneous oedema accumulation with a honeycombed pattern, and muscle compartment enlargement. Magnetic resonance imaging may show diffuse dermal and subcutaneous oedema, variability in regional lymph node size, and increased subcutaneous fat. Duplex ultrasound is useful for examining the deep venous system and supplement or complement of the evaluation of extremity oedema. Ultrasonographic evaluation enables the measurement of the thickness of the skin and subcutaneous tissue. The quantification of the degree and uniformity of the skin and subcutis swelling using ultrasonography may prove a simple, useful, and reliable outcome measure of lymphoedema [20]. Other diagnostic or investigational tools are magnetic resonance lymphography, indirect (water soluble) lymphography, near infrared fluorescent imaging, fluorescent microlymphangiography, dual energy x-ray absorptiometry or bi-photonic absorptiometry, and genetic testing.

Several types of measurements are used to determine the volume of the lymphoedematous limb. Circumference measurement with a tape measure is the simplest and the most commonly used measurement method. Volumetric evaluation with water displacement is also an inexpensive and simple method. Disadvantages of this volumetric technique are decreased sensitivity, observer variability, and the inability to use with wounds and infections. Perometry utilises an optoelectronic device consisting of optoelectronic sensors in order to measure limb volume. It represents an objective evaluation of limb volume and ensures a valid measurement. For clinician diagnosis, limited data are available at this time [20, 21].

Early diagnosis of lymphoedema is very important as it significantly increases the success of the treatment [7]. Nevertheless, it can be debated whether the tools used in advanced assessment are actually advanced or essential in obtaining a diagnosis for the patient. It is often easy to diagnose a patient with a dependency oedema from the clinical questioning and physical examination, but it is much more difficult to draw a conclusion of diagnosis when the patient has a type of primary lymphoedema or questioning leads to other causes [22].

Table I. Differential diagnosis of lymphoedema

Symptoms	Lymphoedema	Lipoedema	Phleboedema
Manifestation	Primarily in one leg with differences between the sides	Primarily symmetrical and almost exclusively in women	Oedema concurrent with evidence of venous disease
Location	Dorsal surface of foot, ankle, and occasionally thigh, sometimes isolated to one region	Lower leg, thigh, hips (foot typically not affected)	Predominantly at the ankle and dependent in nature
Swelling	Hump on dorsal surface of foot. Loss of the leg contours	Collar-like, supramalleolar fat accumulation	Initially retromalleolar, then ascending. Foot rarely affected
Colour	Body colour, but may darken with chronicity	Body colour	Brownish discolouration from haemosiderin and melanin
Induration	Pitting in the early stages, but non-pitting later; Stemmer sign positive	Firm but Stemmer sign negative	Hard but the pitting nature persists. Eventually becomes woody.
Temperature	Cool	Normal to cool	Warm
Sensation	Painless	Painful under pressure in later stages	Painful, itching and throbbing
Heaviness	Evening time	Evening time	Evening time
Complications	Erysipelas, cellulitis, athletes foot, exudation of lymph	Intertrigo, cellulitis, athlete's foot	Venous ulcer, superficial vein thrombosis, haemorrhage
High resolution ultrasound	Subcutaneous tissues in the region of the oedema are thicker and more echogenic. Characteristic echo-free gaps and canals.	Supramalleolar subcutaneous tissues are thicker and very echogenic; prominent echogenic septae	Non-specific oedema. Venous disease findings of reflux, thrombosis, obstruction and occlusion within veins

Phleboedema and lipoedema should be firstly considered in the differential diagnosis of lymphoedema (Table I). The other conditions accompanied by oedema are congestive heart failure, liver cirrhosis, renal disorders, endocrinological disorders, intestinal disorders, and iatrogenic, nutritional and infectious causes (Table II).

Treatment

There is no curative treatment for lymphoedema; however, it is easily managed with early recognition and therapy. Those who do not have therapy tend to worsen quickly and advanced disease tends to be more difficult to treat than early disease. The treatment of lymphoedema aims to alleviate symptoms, restore functionality of the affected limb or body area, and prevent progression and potential complications associated with lymphoedema. Patients with lymphoedema are best treated in specialised clinics; inexperienced staff may delay treatment, or worse, advocate inappropriate treatments [23]. The treatment of lymphoedema is divided into four main topics: Conservative, pharmacological, surgical and other treatments.

Conservative treatment

The most important column in the conservative treatment of lymphoedema still represents the complex decongestive therapy (CDT). This is a multimodal therapy, which consists of 4 components: Compression therapy, manual lymphatic drainage (MLD), exercise, and skin care. The CDT is divided into two phases. Phase 1 (decongestion phase) primarily serves the mobilisation and transporting away the banked protein-rich oedema fluid and seamless transition into Phase 2 (maintenance phase), which serves to preserve the achieved treatment success. The implementation of the CDT should be stage-adjusted, but also depends on the location (head, neck, genital), and on coexisting comorbidities (congestive heart failure, obesity, diabetes mellitus, musculoskeletal disorders, mental illness, etc.). It should be modified for children, elderly patients and those with malignant lymphoedema [24]. The

Table II. Other systemic causes for oedemas in the extremities

Aetiology	Clinical picture
Cardiac	Congestive heart failure
Hepatic	Liver cirrhosis
Renal	Glomerulonephritis, nephrotic syndrome
Endocrinological	Hyper- or hypothyroidism
Intestinal	Ulcerative colitis, enteropathy, malabsorption
Iatrogenic	Medications including anti-hypertensives, nonsteroidal anti-inflammatory drugs, steroids, proton-pump inhibitors, hormones, cyclosporin, immunosuppressive agents
Nutritional	Protein deficiency, malnutrition
Infectious	Cellulitis, borreliosis, filariasis

intensive therapy during Phase 1 of CDT usually takes 4-6 weeks and may be applied in the hospital or outpatient clinics. To achieve the best results, the CDT should take place at least 5 days in each week. Hospitalisation is preferred for some patients, including immobile patients, patients with complications and comorbidities, and those who cannot undergo therapy in everyday regime on an outpatient basis [19, 20]. Phase 2 of the CDT is a long-term maintenance therapy, individualised to the requirements of each patient. It can be outpatient-based or as self-care in selected trained patients. Patients should wear compression garments during the day and compression bandages at night. Intermittent pneumatic compression therapy is sometimes used, but care needs to be taken to ensure that they have appropriate design, action, and pressures (usually 30–60 mmHg, although pressures of >45 mmHg can cause the lymphatics to rupture). The other modalities of the maintenance therapy are MLD, exercise and skin care [25–27]. When the CDT is not successful, situations such as malignant lymphoedema, artificial lymphoedema, breaking the treatment protocol and not using a suitable treatment should be considered. CDT could not be successful also in cases of the lack of compliance and hygiene, misdiagnosis, or reactivation of the cancer.

Satisfactory results are often obtained with conservative therapy, but the effects are temporary without maintenance and continued compression. General care is also important. Patients are advised to avoid even minor degrees of trauma, such as venepuncture, acupuncture, insect bites and blood pressure cuff application on the lymphoedematous arm. Generally, patient education is not one of the four classic components of CDT, but it plays an important role.

Compression therapy

Compression therapy is considered a key component of the CDT, both in reducing the limb volume during Phase I and in helping to control the condition during Phase II. Compression helps to resolve lymphoedema by reducing capillary filtration, increasing lymphatic flow, shifting fluid to uncompressed fields, and breaking down fibrosclerotic tissue [28, 29]. Multilayer low stretch bandages can be left on the affected field overnight for 24 hours in Phase I. One layer bandage is applied during the day only in Phase II. The multilayer lymphoedema bandaging consists of a single protection layer of cotton tubular bandage next to the skin and a soft synthetic wool or foam under-padding. Short stretch bandages have a high working pressure and compressive forces are maximal when the underlying muscles contract. In Phase II, various compression garments and bandages can be utilised. Compression garments and bandages are categorised according to the type of fabric they are manufactured from. The severity of lymphoedema determines the grade of compression needed from the garment (I–IV grades). They can be custom-fit or purchased over the counter in standard sizes. It is important to use the low pressure-short stretch bandages instead of higher pressure-long bandages, leading to the collapse of lymphatics due to excessive compression. Custom-knitted garments offer greater support and are recommended in advanced lymphoedema. The requirement for custom garments must be determined individually; general indications include irregular limb contour and extensive fibrosis. Compression garments should be replaced every 6 months [20]. Compression bandaging and compression garments demonstrate effectiveness in various stages of the treatment of lymphoedema. There are only a few studies directly comparing the effectiveness of these two compression tools. Compression bandaging can result in greater volumetric effect in the initial treatment phase, but compression garments can result in fewer symptoms and better functional status [30].

Manual lymphatic drainage (MLD)

Manual lymphatic drainage is not the same as massage; it consists of intermittent, gentle pressure applied directly on the skin to stretch the very small initial lymphatics, increasing lymphatic vessel contraction, and lymph drainage of the affected field. It has four essential hand strokes which must be circular or spiral in character and with a slow frequency. The central fields are treated first, and then the drainage continues peripherally. A session of MLD begins centrally at the neck and the trunk to clear out the main lymphatic pathways. MLD takes 45–60 minutes and is applied in a descending manner to facilitate the flow of lymph from affected areas to those that are not affected. It has been shown to stimulate lympholymphatic and lymphovenous anastomoses [6, 25, 31].

The results of numerous studies demonstrated the value of MLD when combined with compression in the treatment of lymphoedema [32–34]. These results did not support using MLD alone for the aim of limb volume reduction independent from the CDT. However, in a systematic review, it was reported that MLD alone contributed to an improvement in self-reported symptoms when used in the palliative care setting [35].

Exercise

Exercise is one of the fundamental components of care for patients with lymphoedema. Exercise increases the activity of muscle pump to encourage venous and lymphatic drainage in addition to maintaining or improving a range of movement. The group activity is being increasingly used to assist with compliance, motivation and to increase self-esteem. Exercise programs such as healthy steps and yoga have proven successful for patients with lymphoedema, improving their quality of life [36, 37].

Skin care

Appropriate skin care is essential for patients with lymphoedema in order to avoid the condition worsening and skin infections such as cellulitis and lymphangitis [38]. In recent years, many advances have taken place in wound technology, allowing for improvements in care to treat lymphoedema skin-related problems such as hyperkeratosis, lymphorrhoea and skin maceration. Many dressings

now have specialised technology, such as layers that lock moisture away from the skin and barrier creams, allowing macerated tissue to stay protected. This reduces the requirement for regular dressing changes; however, it does not replace the necessity of daily washing and moisturising of the skin. This situation is particularly important where there are high levels of dryness, skin sensitivity or hyperkeratosis [22].

Intermittent pneumatic compression (IPC)

IPC therapy is widely used in the treatment of lymphoedema as an adjunct to CDT. It is particularly useful in cases that are treated with passive physical therapy (i.e., elderly patients, immobile patients, and patients with serious disabilities) in whom spontaneous/isotonic physical exercise is compromised or not possible. The inflation and deflation of IPC requires pressure that mimics the action of the muscle pump, which is an important mechanism in lymph transport. IPC reduces lymphoedema by decreasing capillary filtration and lymph formation [39, 40]. However, nowadays, the use of IPC with pump devices is controversial due to its adverse effects. These devices extract water from the interstitial space with the help of pressure, but the proteins remain on the same field. Although oedema reduces after application, it can reappear or increase further because the residual proteins in the interstitial space retract the water. Another adverse effect is that it damages lymphatic structures when it is applied with high pressure. The most suitable patients for IPC treatment are those who finish phase 1 of CDT but still have oedema or patients with oedema due to venous insufficiency [41]. In selected patients, the use of IPC may provide an acceptable home-based treatment modality in addition to wearing compression garments [42]. Nowadays, specialised lymphatic pump devices that work with a much lower pressures and slower sequences have been developed, which are compared with widely used venous or less commonly used arterial pumps. These new generation pump devices may be more beneficial for patients with lymphoedema without adverse effects.

Clinical results of CDT

Despite the differences in methodology and protocol, the clear result in most studies was an immediate improvement in limb volume, whether using CDT or a variant. The limb volume reductions obtained in the different studies covered a range (22–73.5 %) [26, 28, 33, 43–45]. The short- and mid-term results of some of the clinical studies are shown in Table III. However, the long-term results of the CDT were harder to detect; only a few reports included follow-up. Kim et al. had a 6 month follow-up and found that 42 % of the subjects had regressed to being 15 % below where they started [32]. Johnstone et al. [34] had a median follow-up of 7.5 months, but a very small sample size (11 patients returned for follow-up out of an initial 82 patients). Of these, 7 cases who reported adherence to their home program had continued to reduce and 4 cases who had not had begun to increase in limb volume again [34]. Mondry et al. had a 12 month follow-up, and also noted limb volume increasing during the follow-up [46]. Vignes et al. had the largest number of cases (n=426) of whom 356 were available for 12 month follow-up. These cases had a home program of wearing compression garments daily and bandaging 3 nights a week (and having MLD 1-3 times a week). There were continuing limb volume reductions of more than 10 % in 28% of these cases [33].

Table III. Early and mid-term results of the some clinical studies on complex decongestive therapy

Clinical study	Volume reduction rates
Kim et al. [26]	43.6 %
McNeely et al. [28]	44 – 46 %
Vignes et al. [33]	38 %
Jeffs et al. [43]	70 %
Yamamoto et al. [44]	59 % for arm lymphoedema, 73.5 % for leg lymphoedema
Pinell et al. [45]	22 % (included patients with active tumors)

Pharmacological treatment

Diuretics are not useful and will not be discussed further, because these drugs only remove water from the interstitial space; therefore, the proteins that remain in the interstitial space retract more water and worsen lymphoedema. According to the 2013 Consensus Document of the International Society of Lymphology, the diuretic agents can be limited used in some selected patients at the beginning of the CDT (Phase I) as an adjunctive therapy. However, it is not recommended at the long-term administration, because they induce fluid and electrolyte imbalance if used for a long time [12].

In studies conducted in the past years, it is stated that benzopyrones (such especially coumarin) stimulate the macrophages, thereby, increasing proteolysis and helping protein catabolism in lymphoedema; thus, lymphoedema may be reduced [47]. However, in a randomised, double-blind, placebo-controlled study with a relatively large sample size, Loprinzi et al. reported that coumarin did not have a meaningful effect on reducing limb size and lymphoedema-associated symptoms. Moreover, they also reported that 6% of the study population experienced coumarin-associated liver toxicity [48]. Although the effectiveness of coumarin is still debated, especially with respect to the risk of liver toxicity, Farinola et al. advocate that toxicity alone should not prevent future investigators from reassessment of the potential benefits of coumarin for the treatment of lymphoedema. The authors suggested that the use of pharmacogenetics could meaningfully lower the risk of coumarin-associated liver toxicity [49]. Hence, further investigations with a rigorous design and larger sample sizes are required for reassessment of the effectiveness of coumarin in the treatment of lymphoedema.

Antimicrobial agents are indicated in some cases, like the treatment of bacterial and fungal infections of the skin, subcutaneous tissue and nails, such as erysipelas, cellulitis, lymphangitis and onychomycosis, all of which worsen lymphoedema. The administration of a prophylactic penicillin or broad spectrum antibiotic is recommended for patients who have more than two to three episodes of infections per year despite optimal CDT. Fungal infections can often be treated with terbinafine or flucanozole. Diethyl-carbamazine, albendazole and ivermectin are beneficial agents to eliminate worms and microfilariaes in patients with lymphatic filariasis. Foot care and hygiene is very important to prevent opportunistic infections [12].

Surgical treatment

The surgical procedures in the treatment of lymphoedema have existed for over a century. Among these, Charles' procedure was the first reported operation in 1912 [50]. This procedure involved an aggressive excision of skin and subcutaneous tissue down to the fascia, followed by skin grafting over the excised area. Charles operation obtained a debulking of the limb; however, it was not an effective procedure at managing ongoing lymphatic stasis. Interventions for the preservation of lymphatic functions were first described by Sistrunk, and then by Thompson [51, 52]. However, the outcomes of these interventions have been frequently unsatisfactory with disfiguring. Therefore, these interventions have largely been abandoned. In contrast, the contemporary surgical approaches in the treatment of lymphoedema now involve much less invasive approaches and involve microsurgical approaches to decrease the excess lymphatic fluid or minimally invasive approaches for the removal of accumulated proteins within the affected extremity. Surgical treatments of lymphoedema have gained popularity in recent years, but it should be understood that the surgical treatment of lymphoedema is reserved primarily for patients who have lymphoedema that is refractory to standard treatment modalities [53].

Vascularised lymph node transfer (VLNT)

VLNT involves the transfer of a healthy pedicled groin flap including the inguinal lymph nodes, to the contralateral inguinal region in the lymphoedematous lower extremity to reroute the lymph drainage pathway. A stable volume reduction was obtained in the lymphoedematous extremity following this procedure. After the first applications of VLNT, numerous case series have been reported [54–56]. As a common result of these case series, the VLNT has been considered a promising procedure. In particular, the volume reductions of lymphoedematous limbs were achieved in many cases after VLNT. Furthermore, all of these studies have shown a decrease in the incidence of lymphoedema-associated infections after VLNT.

The surgical procedure of VLNT is very similar to the perforator flap transfers with the addition of capturing lymph nodes and securing a blood supply to the transferred nodes. The key to the success of VLNT is that it preserves the lymphatic vessels, not solely as conduits but also as functional vessels. The most commonly selected donor areas are the groin, axilla, supraclavicle and submentum. Inguinal lymph nodes are the most commonly used donor nodes for arm lymphoedema, because of the lymph node flap may be combined with abdominal flaps for autologous breast reconstruction. The most common recipient sites for arm lymphoedema are the axilla, and sometimes the elbow and wrist. For leg lymphoedema, the most common donor and recipient area is the groin [57].

As a consequence of a recent comprehensive review study, the authors have stated that although the outcomes of the application of VLNT in the treatment of lymphoedema have been largely positive, further studies into standardised protocols with large sample size are required [58].

Lymphovenous anastomosis (LVA)

LVA is a microsurgical procedure in which lymphatic vessels, frequently with a diameter ranging from 0.1 to 0.6 mm, are sewn to adjacent venules to bypass an area of obstruction and drain excess lymph directly into the venous system. Nowadays, LVA can be performed with minimally invasive technique under local anaesthesia and low complication rates by experienced surgeons in selected lymphoedema patients. The outcomes of the application of LVA in some case series have been reported to be promising [59–61]. The largest series of LVA was reported by Campisi and colleagues. The authors reported over 30 years of experience in the treatment of chronic peripheral lymphoedema by mostly LVA of microsurgical techniques performed in over 1,500 patients. In their series, volume changes were shown, with a significant improvement in over 83% of patients, with an average follow-up of more than 10 years. Additionally, an 87% reduction in the incidence of cellulitic attacks has been shown after microsurgery. They have concluded that microsurgical techniques, especially LVA, should be the therapy of choice in patients who are not sufficiently responsive to non-operative treatment [61].

In spite of the satisfactory outcomes of these reported series, there is a lack of evidence of the net effect of LVA, because all of these studies are retrospective observational studies, and this procedure has been mostly combined with non-operative treatment modalities in the treatment of lymphoedema. Therefore, further studies are required to evaluate the real effectiveness of the LVA.

Lymfolymphatic bypass (LLB)

LLB is an auto-transplantation procedure of healthy and functional lymph vessels from a donor area of the lymph vessels of the affected limb. LLB is usually performed for patients with breast cancer-related lymphoedema; for these patients, the most commonly used donor area is ventromedial thigh. For this purpose, as free lymphatic grafts,

two or three lymphatic collectors can be transferred to the diseased limb. Although studies in the literature have demonstrated the volume reduction in both upper and lower extremities, the improvements in limb size were obtained more easily in the upper extremities than in the lower extremities. Furthermore, this procedure has a potential disadvantage which is a hazard of an iatrogenic lymphoedema in the donor area [62, 63].

Suction-assisted protein lipectomy (SAPL) or liposuction

SAPL or liposuction is a less invasive excisional procedure which allows for selective removal of the solid components of lymphoedema swelling seen in chronic lymphoedema. Numerous studies have proven the effectiveness of the SAPL both short-term and long-term follow up. Moreover, this procedure provides an improvement in the patients' quality of life [15, 64–66]. Complications of the procedure, such as infection and delayed wound healing, are rare. The major limitation of long-term success after the procedure is adherence to lifelong CDT and compression therapy. In spite of the satisfactory outcomes, this procedure does not reverse or slow the pathophysiologic process of the lymphatic system [63].

Other treatments

Low level laser therapy

Among complementary and alternative treatment methods, the low level laser therapy is the only method that has been proven effective in the treatment of lymphoedema by rigorous studies [67, 68]. This method provides limb volume reduction, softens hard and oedematous tissues, and decreases pain, by radiating low amplitude wavelength rays that penetrate into lymphoedematous tissues.

Shock wave therapy

Shock wave therapy is applied to the lymphoedematous limbs because it enhances cellular metabolism, and has anti-inflammatory, vasodilatory and neo-angiogenic effects. This method is implemented as 1000–4000/session shock waves in 1–2.5 atmospheric pressure in a small group of patients with lymphoedema, and volume reducer effect of this method is published as a preliminary report. Pain, irritation, petechiae, haematoma, and oedema are reported as complications [69]. There is a need for further randomised controlled studies with large sample size to determine the effectiveness and safety of this method.

Stellate ganglion blockage

It was reported in a matched cohort study that volume reductions are similar in patients with breast cancer-related lymphoedema by the application of the stellate ganglion block when compared to the CDT [70]. However, there is a need for further prospective studies to generalise the results of this study because there is a small number of patients and it did not include a long-term follow-up.

Kinesio taping

Recent studies have demonstrated that Kinesio taping is an ineffective method for limb volume reduction in patients with lymphoedema [71, 72].

Diet

There is no specific diet for uncomplicated lymphoedema, and there is no benefit of limited protein or fluid intake. It is essential to include vitamins and fibres in a healthy, nutritious diet, as well as reducing calories and lipid uptake, to avoid obesity [12].

Psychosocial support

Psychosocial support is one of the most important components of lymphoedema treatment [12].

Treatment modalities with insufficient evidence of benefits

The evidence supporting acupuncture, hyperbaric oxygen therapy, and the use of botanicals in the treatment of lymphoedema is insufficient [73, 74].

Conclusions

Lymphoedema is a common and progressive disease which causes the deterioration of quality of life. Early and accurate diagnosis is crucial for the proper management of lymphoedema. Generally, the diagnosis of lymphoedema may be established with a complete clinical evaluation; nevertheless, lymphoscintigraphy is often necessary to confirm the diagnosis. The management of lymphoedema remains a complex entity that should be individualised for each patient. CDT with maintenance therapy in the mid- and long-term is reported as the most essential component of lymphoedema treatment in almost all literature. Other medical and surgical treatment modalities are usually needed as complementary and supplementary treatments or when the conservative therapy is insufficient.

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Correspondence address
Ahmet Yüksel, M.D.
Cardiovascular Surgery Department
Bingol State Hospital
Duzagac Street
12020 Bingol
Turkey

ahmetyuksel1982@mynet.com