

Lymphoedema – Up to now – Review –

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ABSTRACT

Lymphedema is defined as the increasing of protein rich fluid in the interstitium which causes chronic inflammation and reactive fibrosis of the affected tissues. A defect in the lymph conducting pathways often leads to primary lymphoedema. Secondary lymphoedema is due to factors arising out of the lymphatic system. Most patients diagnosed with lymphoedema are best treated by conservative measures, especially elastic compression stockings, weight loss, and the careful use of diuretics. The aim of this review is also to highlight the necessity for healthcare services to be reactive and adapted to the needs of patients with lymphoedema, likewise improving their quality of life.

Key words: lymphedema, lymphoedema, trauma, plastic surgery, lymphatic system, vascular disease

INTRODUCTION

The lymphatic system is the third vessel system in the body involved in the absorption of interstitial fluid and in the reaction to infection. More precisely, the lymphatic system transports 10% of filtered fluid from interstitium; transports large molecules such as fats, proteins fats and proteins; produces

lymphocytes; and recognizes and responds to foreign cells, cancer cells. The lymphatic system normally drains subcutaneous tissues to local lymphatic channels and regional nodes. In this regard, the lymphatic system has the next major components:

1. the terminal lymphatic capillaries – dermal valveless, end blindly in tissues which absorb the lymph from the tissues;

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2. lymphatic precollectors – subdermal, with valves, and parallel with superficial veins;
3. the initial collecting lymphatics – are deeper, and resorb fluid which transport the lymph (valves ensure one way flow);
4. the lymph nodes – which act as mechanical filter, and have an immunological role;
5. ducts – thoracic duct, cisterna chyli, and right thoracic duct.

Lymphatic capillaries are blind-ended vessels formed by a single layer of endothelial cells. It is important to point out that the basement membrane of lymphatic capillaries is often absent or commonly fenestrated with positive entrance of interstitial proteins and particles. Therefore, its main function is to remove plasma proteins and fluids which have filtered through the capillaries into the tissue spaces. Lymphatic capillaries join to form collecting lymphatic vessels which are larger vessels with smooth muscle and vasomotor activity. Collecting lymphatic vessels closely follow the veins in the legs and finally release their lymph into the thoracic duct that drains into great vessels in chest. □

DEFINITION AND CLASSIFICATION

Lymphoedema is the development of lymph in soft tissues, interstitial spaces, and subcutaneous fat due to a defect in the lymphatic

system (1,2). The result of this process is the chronic inflammation and reactive fibrosis of the affected tissues (3). This inadequate drainage of lymphatic system may be spontaneously (primary lymphoedema) or secondary to another disease (lymph node excision for cancer; blockage of lymph channels due to infection; fluid overload that overcomes the functional volume of the system). Moreover, the term lymphoedema has now been substituted by lymphopathy – characterized by frequently absence of clinical manifestations of the lymphoedema at physical examination (4). The lymphatic circulation starts from lymphatic capillaries and ends at the subclavian veins. In disease conditions with changed Starling forces and increased capillary permeability, the quantity of fluid filtered out of the systemic capillaries may critically increase in volume and produce oedema. Therefore, lymphoedema results from:

1. mechanical insufficiency due to damage to the lymph vessels or impairment of lymph flow due to paralysis, blockage or inadequacy of lymphatics;
2. dynamic insufficiency in which the lymph flows surpasses the transport ability of the whole lymphatic system;
3. combined insufficiency. It was suggested that lymphoedema is an increasingly pathophysiological process in which the excess accumulation of protein and fluid stimulates inflammation and macrophage activity (5).

According to Kinmoth's classification, the lymphoedema is classified as primary and secondary (6). The prevalence of **primary lymphoedema** is about 1 per 10,000 subjects. Primary lymphoedema may be hereditary (type I Nonne – Milroy hereditary congenital elephantiasis) due to aplasia of the lymphatics, and may also be non-congenital (type II non – congenital familial lymphoedema). Women are affected more frequently than men. On the other side, hereditary lymphoedema is classified into three clinical subtypes according to the age of presentation:

1. “congenital lymphoedema” or “infantile hereditary lymphoedema” (Milroy's disease) – it appears shortly after birth;

Syndrome associated with lymphatic dysplasia:

1. Aagenaes (lymphedema-cholestasis) syndrome
2. Distichiasis (lymphedema-distichiasis) syndrome
3. Dahlberg (lymphedema-hypoparathyroidism syndrome)
4. Fabry's disease
5. Gorham-Stout-Haferkamp syndrome
6. Hennekam's syndrome
7. Klinefelter syndrome
8. Klippel-Trenaunay syndrome
9. Maffucci's syndrome:
10. Melkersson-Rosenthal-Miesscher syndrome
11. Noonan syndrome
12. Trisomy 10
13. Trisomy 13
14. Trisomy 18
15. Trisomy 21
16. Trisomy 22
17. Turner syndrome
18. Von Recklinghausen's fibromatosis
19. Yellow nail syndrome

FIGURE 1

2. lymphoedema praecox, or juvenile hereditary lymphoedema, occurring at puberty (Meige's disease); and
3. hereditary lymphoedema tarda, occurring after the third decade of life (7). Milroy's disease and Meige's disease have usually autosomal dominant inheritance with variable penetrance (8,9).

In addition, primary lymphoedema is most common associated with the next congenital syndromes:

1. Klippel-Trenaunay syndrome presents with haemangioma (95%), hypertrophy of bones and soft tissues (93%), varices (76%), lymphangioma (8%), and pain (32%) (10);
2. Turner's syndrome presents with the absence of an X chromosome in women, dwarfism, dysplasia of mesodermal tissue (kidneys and ovaries), hypoplasia of the pelvis and patella, facial anomalies, lymphoedema due to hypoplastic lymph vessels;
3. Noonan's syndrome presents with dwarfism, skeletal anomalies, late puberty, congenital heart disease, and intestinal lymphangiectasis.

Pathology of primary lymphoedema includes hypoplasia of lymph collectors (most common), hyperplasia of lymph collectors, aplasia of single lymph collectors, and obstruction due to lymph node hypoplasia combined with fibrosis. Association of lymphoedema with chylothorax and yellow nails has been reported in the literature in both familial and sporadic cases (7). However, cases of the coincident occurrence of lymphoedema, chylothorax and pericardial effusion have been reported only infrequently (11-13).

Secondary or acquired lymphoedema represents the majority of lymphoedema cases, precisely 90% cases of lymphoedema from USA. It may be due to a damage process (as surgery, cancer surgery, vein harvest for CABG, infection); trauma (see Figures 2, 3, 4 – a 54-years-old female presented with lymphoedema complicated with cellulitis secondary to a limbs' trauma); external obstruction to lymphatic vessel (tumour, swelling, fibrosis, inflammation



FIGURE 2.
Post-trauma wound on right leg with lymphoedema



FIGURE 3.
Post-trauma wound left leg with lymphoedema in treatment



FIGURE 4.
Regenerating process with epithelium formation of a post-trauma wound on right leg with lymphoedema (on treatment)

– post infection scarring, radiation, retroperitoneal fibrosis, panniculus; hanging fat of abdomen); internal obstruction to lymphatic vessel (tumour cells, large proteins, parasites – filariosis, Fungus, chemical – silica), malfunction of lymphatic vessel (anchoring filaments, valves, dilated, pumping action, dysrhythmic, spasms, paralysed); and temporary overwhelmed lymphatics (standing too long – immobility, airplane; or surgery interventions with the release of inflammatory cytokines, with increased permeability of blood vessels, lymphatic spasms, increased fluid).

Acquired lymphoedema is a common, significant, and often destructive end of successful surgical and adjuvant therapy of breast cancer and other malignancies (14). In the Western world the cancer treatment by surgery or radiotherapy is the commonest cause. Cancer rarely presents with lymphoedema except in advanced cases, such as prostate cancer, where venous obstruction may coexist. In this regard, relapsed cancer should always be considered in someone with limb swelling after evident curative cancer treatment. Lymphoedema manifesting with sudden onset of swelling of one whole leg suggests proximal obstruction. Pelvic causes of venous or lymphatic obstruction such as tumour or thrombosis must be excluded. Both surgery and radiation therapy for breast carcinoma may cause lymphoedema of the upper extremity.

Filariasis is the most common cause of secondary lymphoedema worldwide and should be considered in any patient with lymphoedema who has travelled or lived in an endemic area (15). Not surprisingly, tuberculosis, pregnancy, contact dermatitis, lymphogranuloma venereum, and rheumatoid arthritis, are also likely to cause lymphoedema.

Microarray technology is currently applied to the clarification of endothelial biology in health and disease (16,17), also in the study of gene expression patterns from cutaneous diseases (18) and in non-neoplastic diseases that involve inflammatory or immune responses (19). □

DIAGNOSIS

The clinical diagnosis of lymphoedema also depends on the medical history and typical skin changes. Even though most swelling occurs in the subcutaneous layer, the skin becomes thicker – which is tested by the failure to pinch

a fold of skin at the base of the second toe; skin folds become enhanced, and hyperkeratosis and papillomatosis develop. Generally such skin alterations are named “elephantiasis.” Severity of lymphoedema is based on differences in limb volume and are measured as minimal (<20% increase), moderate (20–30% increase), or severe (>40% increase) (20).

Lymphoedema is generally a painless condition. The most common signs and symptoms of lymphoedema include swelling, tenderness or pain, tingling or numbness, pressure or tightness, heaviness in the limb, frequent infections, fibrotic skin changes, lymphorrhea, decreased mobility, and impaired wound healing. Lymphoedema is characteristically unilateral, and bilateral lymphoedema is always asymmetrical. About 75% of patients have bilateral lymphoedema, and this type may improve spontaneously with increasing age (2,21).

Affected tissues are initially soft, and the lymphoedema may reduce or disappear overnight, but within a year or two the tissues become rigid with deep folds, with a dry roughened skin, and, sooner or later, hyperkeratosis and recurrent cellulitis develops. Patients may complain of stiffness or pain from associated conditions, such as cellulitis, but lymphoedema itself is not painful. Stemmer’s sign represents the grasp of the second toe or second finger of affected limb below the PIP. Pinch the skin and attempt to lift upward. If the skin does not lift, it is a positive Stemmer’s sign and denotes lymphoedema. On the other side, a negative sign does not exclude a lymphoedema. In addition, lymphoedema alone never causes skin ulceration or nerve damage, and other causes must be sought if these are present. Contrasting with the swelling in chronic venous insufficiency the swelling in lymphoedema does not “pit” or no finger notch left with mild local pressure; it involves the foot and toes; it does not ulcerate; it is not relieved by elevation of the leg (when well developed); and it is painless.

The clinical classification of lymphoedema according to Mowlen (22) is still available: stage I: reversible lymphoedema with elevation of the limb and rest in bed for 24–48 hours, pitting oedema with pressure; stage II: irreversible lymphoedema even with prolonged rest, moderate to severe fibrosis in the subcutaneous tissue and non-pitting oedema with pressure;

stage III: irreversible lymphoedema with severe fibrosis in the subcutaneous tissue and lympho-static elephantiasis in the limb.

Lymphoedema should be distinguished from other disorders that cause unilateral leg swelling, such as deep venous thrombosis and chronic venous insufficiency. The differential diagnosis also includes venous oedema, “armchair legs,” and lipodystrophy or lipoedema, lipo-lymphoedema, and phlebo-lymphoedema which is often misdiagnosed as lymphoedema. Lipedema (or lipoedema) of bilateral lower extremity represents symmetrical fatty deposits, with sparing of the foot and ankle, and with absent Stemmer’s sign; with the legs often painful to palpation and easy bruising. Lipo-lymphoedema represents accumulation of oedema fluid in the presence of lipedema; and it is diagnosed by lymphoscintigraphy and indirect lymphography. Phlebo-lymphoedema has similar treatment with lymphoedema, and responds well to graduated compression, weight loss, and limb elevation.

The diagnostic procedures of lymphoedema include Doppler ultrasonography, lymphangiography, lymphoscintigraphy, computerized tomography, and magnetic resonance imaging. Ultrasound is a low-cost and non-invasive technique. Abdominal and pelvic ultrasound and computed tomography can be used to detect obstructing causes, mainly neoplasms. Duplex sonography remains an excellent tool in diagnosis of lymphoedema and show dilated lymphatics in the soft tissues of the leg. Ultrasound contrast agents are available but currently used only experimental. It is based on micro-bubbles which are stable over a period of time. The applications of ultrasound contrast agents are broad, and improve anatomical findings, show tubal patency, assess tumour vascularity, and show focal masses.

Lymphoscintigraphy and lymphangiography are extremely useful to differentiate primary from secondary lymphoedema (23). Lymphoscintigraphy (isotope lymphography) is the best investigation for detecting oedema of lymphatic origin (3). The lymphoscintigraphy has a sensitivity of 70% to 94% and a specificity of 100%, presenting accuracy higher than 90% (24). The mainly indication is the unexplained limb swelling. The test is based on a tracer (radio-labelled colloid or protein, most common technetium-containing colloid) that is injected into the distal subcutaneous tissue into the finger or

toe from both legs. The monitoring process is assured by a regional gamma camera at 10min intervals over next hour (3). In a normal limb the lymphangiogram will show opacification of five to 15min collecting vessels as they join on the lower most inguinal lymph nodes. This tracer may appear within the major lymphatic channels and lymph nodes as well as within the infection site. Measurement of tracer uptake within the lymph nodes after a fixed interval will differentiate lymphoedema from oedema of non-lymphatic origin. In patients with lymphatic obstruction the contrast medium will often reflux into the dermal network, so called “dermal backflow.” The presence of tracer in the skin by dermal backflow specifies lymph reflux and suggests proximal obstruction. Subsequently the weak passage of isotope from the injection site indicates hypoplasia of the peripheral lymphatic system. Thereby, in primary lymphoedema the lymphatic vessels are absent, ecstatic or hypoplastic. Subsequently, in secondary lymphoedema, the lymphatic vessels are usually dilated.

Both computed tomography and magnetic resonance imaging detect a characteristic “honeycomb” pattern in the subcutaneous compartment that is not seen with other causes of oedema. In postthrombotic syndrome the muscle compartment deep to the fascia is enlarged, whereas in lymphoedema it is unchanged. Thickening of the skin is also characteristic of lymphoedema, although it is not diagnostic. Magnetic resonance imaging is more informative than computed tomography because it can detect water.

Classification of edema:

- 1 + Edema hardly evident;
- 2 + A slight indentation after skin is depressed;
- 3 + A deeper indentation, which returns to normal within 5 normal within 5-30 seconds 30 seconds;
- 4 + Limb is 1.5-2 times normal circumference

Stages of lymphoedema:

- Stage 0: clinically not seen, dysfunction present.
 Stage I: decreases with elevation decreases with elevation, no pitting.
 Stage II: pitting, less help with elevation
 Stage III: pitting absent, fibrosis

FIGURE 5

Complications of lymphoedema are fibrosis, lipodermatosclerosis, ulcers, infection, and disfigurement. Particular attention should be paid to the patients with chronic lymphoedema which have a 0.07–0.45% risk of developing lymphangiosarcoma within 10 years (25,26). □

MANAGEMENT

Accordingly, there is a lack of effective treatment strategies in patients with lymphoedema (27). There is no effective drug treatment. Current options include education of patients in prevention of infection, limb positioning, exercise, compression garments and bandages, pneumatic pumps, and lymphatic massage (28).

Most patients diagnosed with lymphoedema are best treated by conservative measures, especially elastic compression stockings, weight loss, and the careful use of diuretics. Low protein oedemas, such as those due to heart failure or hypoalbuminaemia, are soft and are managed by low compression support, elevation, and treating the underlying cause.

Manual lymphatic drainage includes measures as mobilizing fluid, emptying superficial lymph vessels in a standard fashion, with trained therapist. Non conservative therapeutically measures include surgery, lymphatic reconstruction microsurgery, debulking, always followed by conservative therapy.

Physical treatment to reduce swelling is aimed at controlling lymph formation and improving lymph drainage through existing lymphatic vessels and collateral routes by applying normal physiological processes which stimulate lymph flow.

Exercise dynamic muscle contractions promote both passive (movement of lymph along tissue planes and non-contractile lymph vessels) and active (increased contractility of collecting lymph vessels) drainage. Compression (hosiery) combat capillary filtration; therefore acts as a counterforce to muscle contractions, therefore generating greater interstitial pressure alterations. Graduated compression hose reduces the lymphoedema due to the upright posture. Manual lymphatic drainage is a form of massage that stimulates lymph flow in more proximal, normally draining lymphatics to “siphon” lymph from congested areas, particularly trunk. Multilayer bandaging is used as an intensive treatment in combination with exercise to reduce large, malformed lower limbs and permit subsequent maintenance treatment with hosiery.

Pneumatic compression determines softens and reduces limb volume but can effectively displace fluid into trunk and genitalia; hosiery must always be worn afterwards. Elevation of limbs does not stimulate lymph drainage but lowers venous pressure and therefore filtration, allowing lymph drainage to catch up.

Prevention of acute inflammatory episodes as cellulites or lymphangitis is critical because they can cause severe constitutional upset and deterioration in swelling (Figure 6). Care of the skin, good hygiene, control of skin diseases such as tinea pedis, and careful antiseptic dressings after minor wounds are all important. Antibiotics must be given promptly when an acute inflammatory episode occurs. In recurrent cellulitis the only effective treatment is prophylactic antibiotics – for example, phenoxymethylpenicillin 500 mg daily, for an unspecified period.

Drug treatment for lymphoedema includes diuretics which have little benefit in lymphoedema because their main action is to limit capillary filtration. On the other hand, improvement in patients who are taking diuretics suggests that the main cause of the oedema is not lymphatic. The benefit of benzopyrones, such as coumarin or flavonoids, remains experimental.

Surgery is of value in a few patients in whom the size and weight of a limb inhibit its use and interfere with mobility after physical treatment. Surgery is intended either to remove excessive tissue (reducing or debulking operations) or bypassing local lymphatic defects.



FIGURE 6

The surgical treatment of lymphoedema is divided into two approaches: physiologic (or microsurgical interventions) which restore the lymphatico-lymphatic, lymphatico-veno-lymphatic, lymphatico-venous, or lymph node-venous anastomoses (29-31), and excision surgery (the removal of the lymphedematous epifascial tissue) (32). The indications of excision surgery are for chronic advanced cases and lymphoedema unresponsive to physical therapy. The excision surgery of the lower extremity based on the all excisions of the skin and subcutaneous tissues are classically referred as the Charles procedure. The defect is closed with a skin graft (33).

Suction techniques can also be helpful for the exclusion of excessive subcutaneous tissue and can be utilized in concert with skin excision (34). Supporting results with the use of lymphatic grafts, lymphatic anastomoses, and lymphatic venous anastomoses have recently been reported. Other surgical techniques include treatment with removed omental pedicle and myocutaneous flap intertransposition. In the buried dermal flap operation (Thompson procedure), a part of the subcutaneous lymphedematous tissue is removed under the flaps, the flap edge is de-epithelized, and the resulting dermal flap is buried into the underlying muscle compartment. Therefore, the buried flap constitutes an obstacle against deep fascia regeneration (35). Savelle also described a procedure of total superficial lymphan-

giectomy which involved a two-stage removal of lymphedematous subcutaneous tissue and fascia (35).

Microsurgical lymphovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Therefore, the effective procedure that provides the most reliable improvement of lymphoedema with the lowest incidence of complications is broad skin and subcutaneous excision under skin flaps. The more skin and subcutaneous tissue removed, the better the postoperative result.

KEY POINTS FOR HOME

Cornerstones of treating lymphoedema are skin care, exercise and movement, trunclal massage, and support bandaging or hosiery. Also, essential therapeutical measures are daily self massaging of affected limb, daily bandaging of the limb and eventually daily use of compression garment, meticulous attention to hygiene of the arm with daily inspection and use of water soluble moisturizing creams, and decompressive exercises if the patient is not very active or in the normally active patient, vigorous use of the affected arm and elevation when at rest. Continuous therapeutical management include psychosocial support, attention to infection, cellulites, fungal, parasitic, exercise, hydration and weight control. □

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