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Review Article

Lymphedema: A Brief Overview

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Abstract

Lymphedema is an incurable and progressive condition characterized by chronic inflammation, tissue fibrosis, atrophic changes in skin, localized pain and secondary infections. Often classified as primary or secondary based on the underlying causes, lymphedema could affect the upper and lower extremities, genitals, face and trunk and is noticeable initially by soft pitting edema that occurs in dependent positions but is relieved with elevation. Treatment for lymphedema could be conservative or invasive. While conservative treatment of lymphedema focuses on reducing pitting edema through compression, surgical treatment follows three approaches: resection procedures, microsurgical interventions and suction-assisted lipectomy. According to evidence, integrated physical therapy interventions for lymphedema could decrease lower and upper extremity edema by 90% and 26% respectively.

Keywords: Lymphedema; Physical Therapy; Chronic Inflammation

Introduction

Lymphedema is an incurable and progressive condition that occurs when protein-rich fluid accumulates in body tissues due to dysfunction of the lymphatic system [1,2]. It is characterized by chronic inflammation, tissue fibrosis, atrophic changes in skin, localized pain and secondary infections [2]. Lymphedema can be devasting: associated chronic inflammation limits mobility and function and causes disfigurement that can affect a person's physical and mental health, and quality of life [3,4]. Moreover, limb heaviness, limitations in joint range of motion, pain and compromised wound healing are other factors that limits function, ability to perform activities of daily living and social participation in individuals with lymphedema [4]. The goal in treating this condition is to limit the progression of inflammation and prevent infections [5]. This paper discusses the incidence, pathophysiology, etiology, clinical manifestations, diagnosis, prognosis and treatment of lymphedema.

Pathophysiology

The lymphatic system, a part of the circulatory system, is composed of two networked drainage systems which function to remove and return excess fluid from tissues back to circulation [6,7]. The superficial lymphatic system is found in and drains fluid from, the skin and subcutaneous tissues, in an almost parallel fashion to the venous system [7]. Excess interstitial fluid in muscles, tendons, nerves, periosteum, joints and internal organs is drained by the deep lymphatic system which is connected to the superficial lymphatic system by perforating vessels [7]. Lymph capillaries, the most distal unit of the lymphatic vasculature, are highly permeable

open-ended vessels abundant in the dermis [6,7]. Lymph capillaries are two to three times larger in width than blood capillaries and are therefore able to absorb larger particles in the interstitium, like proteins and bacteria [7]. Interstitial fluid, as soon as absorbed by the lymphatic system, is called lymph [6]. Lymph is rich in protein and contains other components such as water, dead or dying cells and cellular components, white blood cells, fatty acids, foreign material and debris [6,7].

In lymph capillaries, fluid moves from regions of higher lymphatic pressures to regions with lower pressures [7]. From the lymph capillaries, lymph flows first to precollectors, then to lymph collectors and progressively through larger vessels to lymph nodes in regions of the body [6,7]. In lymph nodes, specialized white blood cells called lymphocytes support the body's immune function by identifying and destroying foreign cells, and therefore, lymph node fibrosis or lymphadenectomy could obstruct normal lymph flow and increase susceptibility to local infection [7,8]. Anastomoses between lymph collectors allow supplemental connections across regional lymph nodes thereby creating an alternative lymph drainage pathway [7]. Normally, lymph from the left half of the body, genitals and the right lower extremity, drains into the left subclavian vein majorly through the thoracic duct [7,8]. While fluid from the right upper extremity, right side of head and neck flow through the right lymphatic duct into the right subclavian vein [6,7].

Actually, 2 to 4 litres of fluid enters the interstitial space through arterioles [6]. While 90% of interstitial fluid is drained by venules, the remaining 10% is drained by the lymphatic system [6]. In normal circumstances, the amount of fluid entering the interstitial space is equal to the amount fluid drained from it [3]. Lymphedema results from a disruption in this entry-exit balance following dysfunction in lymphatic transport, or lymphatic insufficiency, either due to increased influx of fluid into the interstitial space or reduced ability of the lymphatic system to drain fluid or both [3,6,7]. Dynamic insufficiency occurs when the lymphatic system is unable to adapt to increased lymphatic load, whereas mechanical insufficiency results from an inability of the lymphatic system to cope with normal lymphatic load [7]. The ensuing lymphatic stasis causes accumulation of protein rich fluid in the interstitium leading to inflammation and other clinical manifestations of lymphedema [3].

Etiology and incidence

Lymphedema is often classified as primary or secondary based on the underlying causes [6]. Primary lymphedema occurs due to congenital or familial developmental vascular deficiencies in the lymphatic system and occurs in only 1% of all cases of lymphedema [3,6,7]. Secondary lymphedema, the more prevalent type of lymphedema, is acquired and results from lymphatic system dysfunction caused by disease processes or iatrogenic procedures [3,6]. Whereas congenital lymphedema is observed clinically at birth or during the first two years of life, other types of primary lymphedema manifest later in life following a minor injury such as an ankle sprain [3,6,7]. Milroy disease, a familial type of congenital lymphedema, causes bilateral lymphedema of the lower extremities, and intestinal lymphangiectasia and cholestasis [3]. Lymphedema that manifests before an individual is 35 years old is called *lymphedema praecox*, while lymphedema occurring after 35 years of age is called *lymphedema tarda* [6] Meige disease, a familial lymphedema praecox that manifests at puberty, affects girls more than boys and majorly causes inflammation of the foot and ankle [3,6].

Other familial types of primary lymphedema include Klinefelter syndrome, Klippel-Trenaunay syndrome, Lymphedema distichiasis, Noonan syndrome, Prader Willi syndrome and Turner syndrome [7]. An uncommon type of congenital lymphedema called lymphangiomas, presents as benign cystic malformations of the lymphatic system [6]. Primary lymphedema can also be classified, based on the type of lymphatic vessel abnormality, as aplasia (absence of lymphatic vessels in a body part, hence no lymphatic drainage), hypoplasia (narrow lymphatic vessels) and hyperplasia (wide lymphatic vessels and lymph node fibrosis) [7].

Across the world, filariasis is the most prevalent cause of secondary lymphedema [6]. It affects 129 million people worldwide [7] and occurs following infection by *Wuscheria banrofti,* a nematode that migrates to and resides in the lymphatic system obstructing lymphatic transport [3]. Filariasis causes a severe and disfiguring type of lymphedema called elephantiasis [7]. In the Western world however, lymphedema most often results after iatrogenic procedures that affect lymphatic flow including mastectomy, lymph node biopsy, radiation therapy, and lymph node dissection [3,7] Lymphedema is often associated with a variety of cancers including breast, urologic, lymphoma, gynecologic, and melanoma, [3] and may develop up to 30 years following cancer treatment [7]. Lower-extremity lymphedema is usually linked to chronic venous insufficiency, obesity, malignancies, melanoma, infection, and renal failure [9]. Less common than lower-extremity

lymphedema, most cases of upper-extremity lymphedema are due to breast cancer treatment and lymphedema occurs after in 24% - 49% of cases post-mastectomy and in 4% - 28% of cases post-lumpectomy. Moreover, 7% - 77% of patients who undergo axillary node dissection develop breast cancer related lymphedema (BCRL). It is assumed that for breast cancer patients who develop lymphedema, 80% of them will manifest the condition within the first 3 years of treatment [7]. Worldwide incidence of lymphedema is approximately 200 million people worldwide and in the United States, about 3 million; while prevalence of primary and secondary lymphedema are 1 to 100,000 and 1 to 1,000 individuals respectively, with females more affected than males [9]. Obesity, trauma and infection are major contributory factors that increase risk of developing lymphedema [3].

Clinical manifestations

Lymphedema can affect the upper and lower extremities, genitals, face and trunk and is characterized initially by soft pitting edema that occurs in dependent positions but is relieved with elevation [3,7] It can manifest unilaterally or bilaterally [9] As the condition progresses, there is fibrosis of subcutaneous tissues and hypertrophy of adipose tissue, [3] the skin becomes indurated and edema may not resolve with elevation [7,9]. Lymphedema is considered irreversible when edema becomes nonpitting [9]. Individuals with lymphedema may complain of discomfort and heaviness of the body part, and different types of pain including deep ache or pressure, stretch pain, neuropathic pain and pain due to infection or inflammation [7]. Chronic lymphedema could develop into elephantiasis nostras verrucosa, lymphorrhea, recurrent cellulitis, skin ulcerations, impetigo, papillomatosis, and cutaneous angiosarcoma [3]. Other changes in the integumentary seen in lymphedema include xerosis, hyperkeratosis, hair loss, deep skin folds, lichenification, vesicle or blister formation, dermatitis, infections, and tinea pedis [7].

Medical diagnosis

Diagnosis of lymphedema is normally made after clinical evaluation, and physical examination for the clinical manifestations listed in the section above [2]. Physical examination could comprise skin inspection, palpation, assessment of joint range of motion, circumferential and volumetric measurements and neurological examination [2,6]. Familial, trauma and surgical history are critical for arriving at a diagnosis [6]. In addition, other history questions can include duration, if edema started proximally or distally, presence and type of pain, paresthesia, progression of the condition (slow or rapid), list of medications being used, co-morbid conditions such as diabetes, cardiac insufficiency, chronic venous insufficiency, thyroid diseases and rheumatic diseases [2]. The Stemmer sign, an inability to pinch the skin on the dorsum of an edematous second digit, is pathogonomic of lymphedema [3,7,9]. Difference in circumferential or volumetric measurements of greater than 2cm or 200ml, respectively, between affected and non-affected extremity can be used to confirm diagnosis of unilateral lymphedema [6]. Non-invasive methods useful for diagnosing lymphedema include biometric impedance analysis (body composition analysis), perometry and tonometry [3,7]. Additionally, lymphoscintigraphy, magnetic resonance lymphangiography, near infrared fluorescence imaging, ultrasonography and computed tomography, can also be employed in lymphedema diagnosis [6]. Considering differential diagnosis, lymphedema can be confused with other causes of edema in the extremities such as morbid obesity, lipedema, hypoalbuminemia, myxedema, cardiac/renal failure, drug induced edema and chronic venous insufficiency [9]. A staging system used to classify lymphedema proposes stages and descriptors of the disease as follows: Stage 0 - latent, Stage 1 - reversible, Stage 2 - spontaneously irreversible, Stage 3 - lymphostatic elephantiasis [3,7].

Treatment

Lymphedema could be treated through surgical and non-surgical options [6]. Conservative treatment of lymphedema focuses on reducing pitting edema through compression [3]. Complete decongestive therapy is considered the gold standard of non-surgical treatment of lymphedema and includes procedures that could be performed by physical therapists such manual lymph drainage and bandaging [1,2,6]. Physical therapy interventions include skin and local wound care, and therapeutic exercise (positioning, active range of motion, flexibility exercises, aerobic and anaerobic exercises, integrated therapeutic exercise approach) to reduce edema, enhance lymphatic and venous return, increase lymph angiomotricity, reduce fatigue, improve range of motion, flexibility and strength [7]. Physical therapists also use manual therapy techniques such as manual lymphatic drainage to increase lymph formation, reroute stagnated lymph and move lymph proximally [3,7]. Multilayer inelastic bandaging and compression therapy have been found to reduce edema by 31% to 46% respectively [3]. Other non-surgical treatments include the use of compression garments

and devices, kinesiotaping, advanced pneumatic compression and low-level laser therapy (available evidence about its effectiveness is limited) [6,7]. One study [9]. concluded that kinesiotaping of the upper extremity in breast cancer induced lymphedema (BCIL) significantly reduced limb circumference, hand grip and quality of life. In their systematic review Johnson and Damarell [4] highlighted several studies that associated land based exercises with improved quality of life, strength, fitness, function, subjective symptoms, and reduced fatigue in patients with lymphedema. The authors however could not directly attribute all these positive changes to the exercises since subjects in control groups also improved. Patient education, diet control and nutritional supplements are useful disease modifying factors [2,3,7].

Medical interventions in lymphedema addresses the management of risk factors such as obesity, and the prescription of medications for pain (analgesics), infection (antibiotics), and inflammation (topical cortiocosteriods) [7]. Pharmacological agents such as benzopyrones are also used to prevent protein accumulation in inflamed tissues [3]. Broadly, surgical treatment can be grouped into three approaches: resection procedures, microsurgical interventions and suction-assisted lipectomy [3]. Resection which involves removal of lymphedematous tissues (subcutaneous tissues and skin) does not address underlying pathology rather it serves to improve comfort through volume reduction [3,6]. Microsurgical interventions which aim to address pathology by creating alternative lymphatic drainage pathways, include lymphatic-venous anastomoses, lymph vessel bypass surgery, and lymph node transplantation and are performed by highly specialized facilities [3,6,7]. Liposuction, the least invasive of the surgical techniques, involves the removal of subcutaneous fatty tissue in affected extremity using suction-assisted lipectomy cannulas and as shown good postoperative results with significant improvement in limb size and other symptoms [3].

Prognosis

Accurate and timely diagnosis of lymphedema and early intervention are associated with improved outcomes [6,7]. Evidence shows that integrated physical therapy interventions are beneficial in the management of lymphedema and there are reports of up to 90% decrease in lower extremity edema over an 8-week period and 26% decrease in upper extremity edema following physical therapy treatment of lymphedema for 4 weeks [7]. Lymphedema in its early stages (0 and 1) is reversible, however, in the later stages prognosis is complicated by comorbidities and complications.

Conclusion

Lymphedema is a progressive debilitating condition caused by lymphatic system compromise and characterized in its chronic stage, by disfiguring swelling in the extremities. It negatively impacts not only an individual's physical health but also their mental health and quality of life. Despite lymphedema's impact on patients' physical and psychological health, it is still underdiagnosed and undertreated [3]. It is diagnosed clinically after comprehensive history, physical examination, tests and measurements and imaging techniques. Compressive decongestive therapy, which aims to control edema and ensure adequate skin and wound care, is the gold standard for conservative lymphedema management following which surgical interventions could be pursued. Prognosis of lymphedema varies depending on the stage of the disease and the associated comorbidities. Therefore, treatment should be adapted to the stage of the disease and should also address the psychological dimension of the condition.

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