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Lymphedema – An Overview

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ABSTRACT

The junction of tubules, thymus, tonsils, spleen, lymph nodes, diffuse lymphatic tissue, lymph nodules and vessels compose the lymphatic system, which unidirectionally collects the lymph from the interstitial space, leading it back to the venous circulation. The process where there is an imbalance between lymph uptake and conduction, causing it to stagnate in the tissues, is called lymphedema, which can be divided into congenital or late. Once the lymphedema installation begins, acute inflammation begins, followed by structural changes in the tissue, the deposition of repair tissue and the gradual evolution to a chronic inflammatory profile and once the lymphedematous process is established, it is not possible to achieve remission, leaving only palliative actions that reduce discomfort and attenuate the evolution of the condition. Several researches currently employ cell therapy in various approaches to treat lymphedema.

Keywords: Lymphatic system, Lymphedema, Circulation, Lymph, Anatomy

INTRODUCTION

Among the various circulatory disorders that cause extremity edema there is lymphedema, characterized by the accumulation of interstitial fluid, resulting from disorders in the lymphatic system. This system anatomically arranged throughout the body, with its collecting vessels, pre-collectors and ganglia or lymph nodes, captures and drains fluid from the interstitial environment and, on average, conducts 100 grams of proteins per day. The flow in the thoracic duct is around two liters a day. Under extreme conditions of its function, the thoracic duct, which is the main driver of lymphatic return flow, can evacuate from 20 to 30 L of lymph per day. The lymphatic system acts by differing oncotic and hydrostatic pressures, resulting in the metabolic balance of the interstitium [1].

Peripheral lymph production and lymph drainage to the veins form a very subtle balance, resulting in lymphatic transport. A continuous layer of smooth muscle in the lymphatic collectors permits the vessels to contract between the valves. This results in a unidirectional flow of the lymph. An efficient drainage of the lymph results of extremities muscle contractions, breathing movements and passive body setting. The flow through lymph nodes is crucial, once it prevents peripheral intercellular fluid, macromolecular proteins and cell debris accumulation, as it occurs in lymphedema [2].

Lymphatic System Anatomy

The circulatory system results in the fusion of numerous tubules and vessels, which are constantly traversed by blood and lymph, thus distinguishing the blood vascular system and the lymphatic vascular system, and the latter system is attached to the venous part of the vascular system [3,4]. The lymphatic system has its embryonic origin in the mesoderm and it represents an auxiliary drainage pathway of the venous system, returning to the bloodstream fluid from the cellular interstitium, called lymph [5,6]. Lymphatic vessels are composed of capillaries, vessels, ducts and lymphatic trunks and are present in almost all body tissues except the deepest parts of the peripheral nerves, bones, superficial parts of the skin, and the central nervous system [7,8]. The lymphatic capillaries are arranged in closed networks that spread throughout the body, giving rise to lymphatic vessels, which have physical properties of stretching and contractility. Inside these vessels, with the exception of the

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capillaries, are found valves that allow the passage of lymph and prevent its reflux [9] and ensure that the lymph flow is unidirectional, so as to converge in the larger collecting ducts, so that it can be led to the heart [10,11]. The lymphatic vessels, as well as the venous ones, are composed of three tunics: adventitia, medium and intimate, however, the intimate and medium tunics have a smaller thickness in the lymphatic system [12].

The lymphatic system primary function is to harbor cells of the immune system, which are responsible for recognizing exogenous or abnormal endogenous molecules such as viruses, bacteria or other invading microorganisms[13], as well as lymph transport, a colorless and viscous liquid, which composition is similar to the body part tissue liquid from which it originates [4,7]. It contains lymphocytes, macrophages, red blood cells, proteins and other cells [14]. Unlike the blood, lymph does not have a specific organ that is responsible for its pumping, so lymphatic flow is relatively slow compared to blood flow. Two factors are directly responsible for the velocity and intensity of lymphatic flow: The colloidosmotic pressure exerted by the interstitial fluid and the degree of lymphatic pump activity, which consists of lymph ejection through muscle contraction, fluid movement from external pressure, decubitus or gravity [1,14].

The lymphatic system is also composed of lymphatic organs such as the thymus, tonsils, spleen, hemal lymph nodes, diffuse lymphatic tissue and lymph nodes present in many mucous membranes [15,16]. Particularly in the neck, armpit, and inguinal regions interposed in the lymphatic vessel pathway are lymph nodes, lymph nodes that act as a barrier or filter against the penetration of microorganisms, toxins or foreign substances into the circulatory stream [10,17].

The lymphatic system performs as an overflow apparatus, once it returns proteins and excess of fluid volume from the interstice [14]. Consequently, the lymphatic system also performs a vital function in regulating protein concentration, volume, and pressure of the interstitial fluid **(Figure 1)**. The fluid captured by this system slowly returns to the venous system and the general circulation through the lymphatic ducts that relates to the jugular vein or cranial vena cava [13,18]. Numerous authors report that sometimes small lymphatic vessels can enter veins directly [15,19].

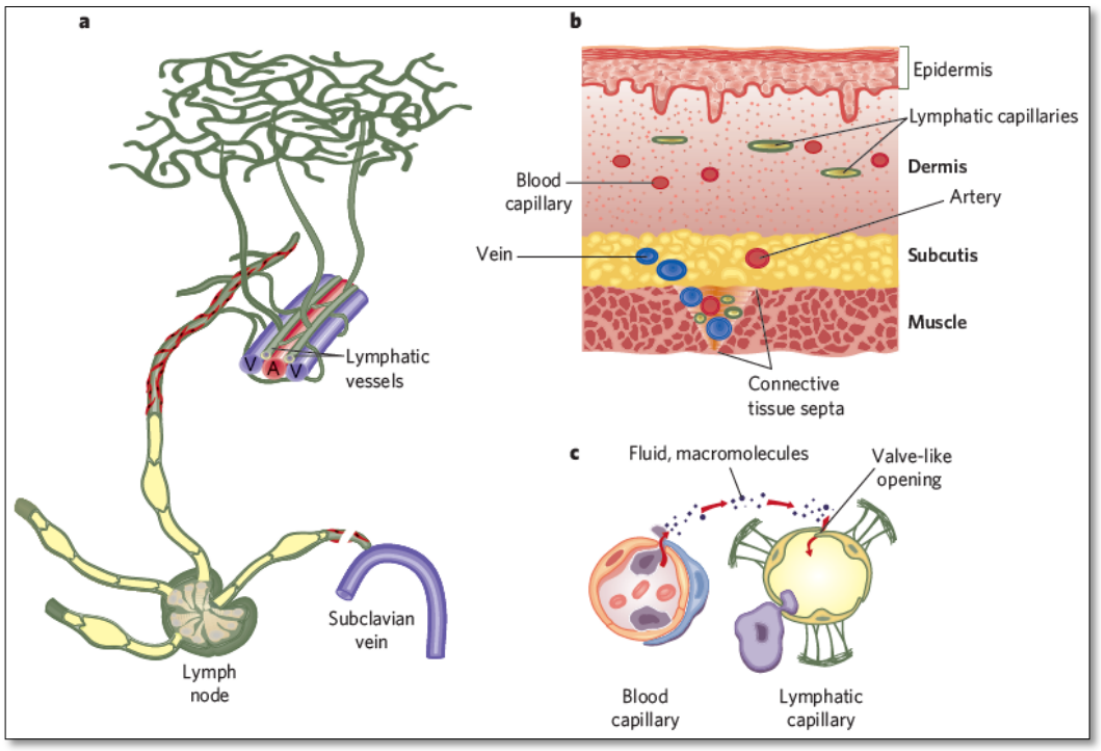

Figure 1. Organization of lymphatic vasculature. A) Interstitial fluid, collected by the initial lymphatic capillary plexus, is transported by pre-collector lymphatic vessels to larger collecting lymphatic vessels and returned to the circulation through the thoracic duct. Collecting lymphatic vessels have smooth muscle cell coverage (red) and luminal valves to propel and maintain unidirectional lymph flow. Deep lymphatic vessels run along arteries and veins. B) Schematic cross-section of skin, showing the relative positions of blood and lymphatic vessels. C) Mechanism of interstitial tissue fluid uptake by a lymphatic capillary.

The large molecules, which do not circulate through the blood capillaries, are collected by the lymphatic capillaries, which allow the passage of water, proteins and crystalloids. From the lymphatic capillaries, the lymph follows through the vessels, leading into the lymphatic trunks, until they are released into medium or large caliber veins [4,13,20].

The role of the lymphatic system is of paramount importance because of its functions in lymphoid cell formation and transport and circulatory balance, such as resorption and transport of fluid and protein load excess in the interstitial space [14,21].

Plasma components, extravasated white blood cells and particulate matter, such as bacteria, enter the lymphatic vessels through loose valve-like openings. Lymphatic vessels are linked to the extracellular matrix by anchoring filaments. The latter are very thin (4-10 nm) fibrillin containing filaments, which are inserted into the endothelial cell plasma membrane. Anchoring filaments prevent vessel collapse in conditions of high interstitial pressure [22].

Edema

Regarding edema formation, some authors point out that the distinct body tissues are kept together completely by the fibers of the connective tissue [12]. However, in many parts of the body, the fibers of the aforementioned tissue are very fragile or even nonexistent. This happens mainly where tissues slither over one another, such as the skin slithering over the back of the hand, or over the face. Even in these locations, however, the interstitial fluid negative pressure, which essentially consists of an incomplete vacuum, holds the tissues together. When tissues miss their negative pressure, fluid amasses in spaces, and a disorder called edema occurs [10,12,14].

Under normal conditions, a minor quantity of interstitial fluid tends to remain in the tissues beyond that which is transferred back into the bloodstream by the lymphatic system. If this fluid and plasma proteins accumulate in excess, the tissues swell, producing a condition called edema, hence the term lymphedema, thus referring to the accumulation of more than physiological amounts of fluids and proteins in the interstitial spaces or cavities of the body. Thus, edema is a consequence of an increase in forces that tend to move fluids from intravascular to interstitial compartment [23,24]. It can be caused by a number of factors, including: elevated venous pressure, decreased arteriolar resistance, reduced plasma oncotic pressure, improved capillary absorptivity, lymphatic uptake and return blockade, lymph node blockage by neoplasia, infection, lymph node agenesis or even congenital abnormalities in vessels, other organs of the lymphatic system or surgical ablation [25].

Lymphedema

Among the various types of edema caused by circulatory and/or lymphatic system disorders, there is the lymphedema [26], which is a clinical manifestation of lymphatic system insufficiency, with consequent lymph transport disorder; a quantitative problem between lymphatic flow and transport capacity [27,28].

Concurring to an established view, an discrepancy between lymphatic load and transport capability leads to protein and fluid accumulation in the interstitial area, leading to edema development [15,26]. Intumescence causes distress and incapacity, but an even major risk is concealed in structural and functional modifications within recurrently lymphedematous tissue [26,28]. Additionally, we can say that swelling is partly a consequence of increased osmotic pressure tissue and consequently leads to changes in skin architecture and even deeper subcutaneous tissues [27,28].

In chronic cases, there is an accumulation of fibroblasts, adipocytes and keratinocytes in the edematous tissue transforming the primarily swollen smooth tissue into a fibrotic firm bulk with fatty deterioration and a rigid and thick skin [22,26].

Chronic impairment of total or partial lymphatic circulation, resulting in an imbalance of lymphatic transport, leads to lymphedema. Condition currently without complete remission, which over time potentially harms the tissues directly involved, compromising the functioning of limbs and organs, which commonly causes physical, psychological and locomotion damage to patients [28-31].

The presence of lymphedema leads to a reduction in the circulation of antigen presenting cells and other immune cells to the lymph nodes and thus those cells diminish their ability to execute their immune reconnaissance function to protect the host against stranger antigens. Consequently, tissues distressed by lymphedema are disposed to inflammation and infection, and in this case, usually mononuclear cells, inflammatory process characteristics have been found [22,24,26,28,30].

Ultimately, there may be subcutaneous tissue thickening, fibrosis, though the processes of this alteration are not yet well comprehended. Interstitial tissue pressure may further failure of the veins, further exacerbating the condition and, in critical cases, amputation is required [28,30].

Thus, in addition to its function of lymphatic drainage of fluids and interstitial capillary proteins back into the venous circulation, the lymphatic system performs a fundamental part in the immune reply within the circulation of cells of the immune system and represents an escape pathway to tumor cell metastasis [2,32–34].

The onset of lymphedema occurs after exhaustion of all compensatory devices of the lymphatic system, such as collateral circulation, lymphatic dilation, lympho-lymphatic or lympho-venous neoanastomoses, increased transport capacity and increased cellular metabolism [18,35].

The clinical manifestation of lymphedema is more frequent in the extremities, but may also affect head and neck, trunk, internal organs and genitalia. Lymphedema can result in numerous complications, the most problematic being recurrent infections in the affected region due to decreased immunity and significant limitations in movement and normal function due to the large size that the affected limb or site may reach [13,27,36].

Lymphedema can be classified into primary or secondary (acquired) according to the disorders causing lymphatic insufficiency [37–39]. Primary lymphedemas result from morphological and functional abnormalities, including hypoplasia or aplasia of large collecting vessels, aplasia of peripheral lymphatic vessels, valvular incompetence or fibrosis and agenesis or insufficient number of lymph nodes [7,13,40].

In human medicine, primary lymphedema is classed corresponding to the age at which it first appears in hereditary lymphedema or Milroy's disease appearing at birth or until the first two years of age; Early lymphedema or Meige's disease is the most commonly identified at puberty, but may also appear up to 30 years; and late lymphedema that usually arises after 35 years of age [13,41-43]. Clinical manifestation of primary lymphedema occurs through anxiety, depression, adaptation problems and professional, domestic, social and sexual difficulties [27,44-46].

Secondary or acquired lymphedema, which is more common, may occur due to a rupture or obstruction of the lymphatic pathways due to a pathological process usually caused by parasites or trauma, or as an outcome of surgery, neoplasia, infection or radiotherapy [27,28,47]. Axillary lymph node dissection in breast cancer removal surgery and filariasis are the most common causes of secondary lymphedema in humans [13,16,46].

In developed countries, secondary lymphedema occurs mostly because of cancer surgery, especially in vulva cancers (20 to 49%), breast cancer (30%), cervix cancer (20 to 49%) and also in extremity melanomas (20%) [2,48]. A great number of surgical procedures have been suggested over the years to reduce the incidence of lymphedema, but none have shown long-term innovative results [2,48].
In order to improve the survival rate of patients undergoing cancer surgery, it is necessary to remove the lymph nodes, thereby stopping lymphatic drainage, thus the body fails to carry the full lymphatic load, and lymphedema occurs [16,49]. In those patients where surgeries consist of the removal of many lymph nodes, there is a need for postoperative chemotherapy and radiotherapy, thus increasing the rate of lymphedema development [2,16].

Surgical intervention is an alternative, but it may be refractory in most treatments [26,50]. Several changes in procedures involve radical incision of the skin and subcutaneous tissue. Other surgical options are the creation of lympho-lymphatic or lymphatic anastomoses[51-54]. However, these surgical options have several complications, including closure failure, hypertrophic scarring, loss of sensitivity, worsening edema in the distal portion and limb deformation have already been cited [35,55].

Some uncommon cases of long-lasting lymphedema may be intricate by a local occurrence of a malignant tumor, for example lymphangiosarcoma, which may be either sclerotic plaques or multicenter injuries with bluish nodules or bullous modifications [9,14]. Other cutaneous neoplasms have been seen in association with chronic lymphedema [2,16].

It is noteworthy that more than one million women around the world develop breast cancer each year [2,56,57]. For most of them, the only treatment is surgical removal of the breast since this disease is potentially able to evolve to death. As breast cancer cells diffuse through the lymphatic vessels, at the moment the breast is parched, local lymph nodes involved in the axilla and part of the its lymphatic system are commonly withdraw and therefore lymph drainage is often discontinued, causing swelling of the arm as a result of lymph collection (lymphedema). Arm edema following surgical intervention for breast cancer is the main cause of lymphedema in the US, and the overall occurrence of secondary lymphedema can be mainly attributed to filariasis affecting more than 90 million people [2,30].

PROSPECTS

Lymphedema is a long-lasting and unremitting disorder that inclines to considerable morbidity and loss of function. This disease has no cure and in the long term it leads to physical and psychological complications for the patient and a major defy for doctors [27,30]. We can say that it is unimaginable to think that nearly 400 years after the discovery of lymphatic vessels, there is still no cure for lymphedema and contemporary medical practice still depends on old processes e.g. manual lymphatic drainage through massage, limited to physiotherapy interventions and edema volume

reduction. These procedures at best deliver only limited relief to the affected persons.
Moreover, as a conservative measure it does not assurance in long term the disappearance of apparently irremediable fibrosis. For this reason, there has been considerable attention in the recently emergent study of growth factor-mediated use in lymphangiogenesis as well as the association with cell therapy using stem cells [2,30,36,42,46].

The full pathological manifestation of lymphedema is complicated and largely misunderstood. Thus, better understanding of the molecular mechanisms of the disease and the signs subjacent the changes that describe the inflammatory process may provide new perspectives for the treatment of lymphedema. However, the progress of research in the field has been encumbered by the absence of adequate experimental model [2,19,30,32].

Currently the most appropriate model is the mouse acquired lymphatic insufficiency model [32,58-60] but historically the first models were made in dogs because they are more similar to humans and with this it was believed to obtain a more reliable and effective model. In contrast, the models had a great inability to reproduce the disease and, in addition, the interposition of foreign bodies caused the breakage of the wound and prevented the use of animals due to its brutal weakness. Most experiments were performed using surgical, radiotherapy or toxicological techniques. In addition to dogs, rats and rabbits, mice are also more commonly used [2,30,35,36,61-63]. Currently therapies associated with angiogenic factors or stem cells as well as association with biomaterials have been tested to improve patients' quality of life [35,42,64].

CONCLUSION

The lymphatic system is formed by primary lymphoid organs (bone marrow and thymus) where lymphocytes are produced and matured, secondary lymphoid organs, known as lymph nodes, where lymphocytes are stored, lymphatic vessels, lymphatic ducts and capillaries, lymph nodes, sites where lymph production and transport occur, respectively. Lymph is a clear liquid, with a blood-like constitution except for the absence of red blood cells in the region and a prevalence of lymphocytes as leukocytes (99%) whereas in blood there is a total of 50% of total leukocytes as lymphocytes in its constitution. The formation of lymph comes from the diffusion of blood capillaries to lymphatic capillaries, its flow is unidirectional which allows a very effective transport towards the great thoracic veins and then to the common thoracic duct, where macromolecules are replaced, especially proteins allowing the maintenance of oncotic pressure in the body. This delicate system can be altered due to poor filtering of lymph fluid by the lymph nodes causing a change called lymphedema. Lymphedema is defined as primary when there is lymphatic hypoplasia or secondary when there is rupture or blockage of lymphatic vessels, in both occasions there is lymph accumulation in certain tissue, usually in places more susceptible to the action of gravity (lower and upper limbs) especially.

Secondary lymphedema is very common compared to primary lymphedema and its main causes are surgery, especially for lymph node removal, radiotherapy, trauma, lymphatic obstruction and in developing countries lymphatic filariasis. The edema is most often unilateral, tends to increase at high temperatures, in a static position subject to gravity for a long time (long flights) and in some cases may affect patient movement. Lymphedema can cause physical and psychological distress, especially when it comes from drug or surgical treatment. Cure is uncommon, in fact, massage and lymphatic drainage are apparently the best ways to treat secondary lymphedema and preventive measures to prevent the development of lymphedema should be adopted.

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AUTHORS' CONTRIBUTIONS

All authors were responsible for collecting data, writing and reviewing of this article.

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All authors declared that there are no conflicts of interest.

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Not applicable.

CONSENT FOR PUBLICATION

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