

# Current concepts and future directions in the diagnosis and management of lymphatic vascular disease

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## Abstract

Despite the central, complex role for the lymphatic system in the maintenance of human health, the biology of this important and complex vasculature has been relatively under-investigated. However, the last decade has witnessed a substantial growth in the elucidation of lymphatic structural biology and the function of this system in health and in disease. These newly gained insights can be used to formulate our evolving concepts about the diagnostic and therapeutic approaches to patients with lymphatic vascular disorders. In lymphedema, there is a spectrum of disease that extends from primary (heritable) to secondary (acquired) causes. Once detected, the presence of lymphatic edema mandates very specific modalities of intervention, predominated by physiotherapeutic techniques. In addition, a physiological basis for adjunctive, intermittent pneumatic compression has been established, and these modalities may be indicated in selected patient populations. The acknowledgement of a unique biology in lymphatic edemas is, increasingly, guiding research efforts within this field. Increasing investigative attention is being directed toward animal models of lymphatic vascular disease. As insight into the complex biology of the lymphatic vasculature continues to expand through focused biomedical investigation, the translation of these mechanistic insights into targeted, rationally conceived therapeutics will become increasingly feasible.

## Keywords

edema; lymphedema; review; risk factors; vascular diseases

## Introduction

It is somewhat paradoxical to acknowledge that, despite the central, complex role for the lymphatic system in the maintenance of human health,<sup>1</sup> the biology of this important and complex vasculature has been relatively under-investigated.<sup>2–5</sup> However, the last decade has witnessed a substantial growth in the elucidation of lymphatic structural biology and the function of this system in health and in disease. These newly gained insights have informed our evolving concepts about the diagnostic and therapeutic approaches to patients with lymphatic vascular disorders.

Lymphatic vascular insufficiency is a common, under-acknowledged problem in the population. Most commonly, the manifestation of this vascular dysfunction is lymphedema, the regionalized tissue edema that results from either inherited or acquired lymphatic disease. In addition, there are a variety of benign and malignant structural anomalies, including lymphangiectasias, lymphangiomas, inflammatory pathologies, and others, that commonly distort normal lymphatic function. In the presence of these disorders, and reflecting the affected region of the body, loss of normal biological properties can lead to one or more of the predictable sequelae: loss of tissue fluid homeostasis, impairment in immune traffic, or disturbances in lipid and protein reabsorption for the gut lumen.<sup>1</sup>

## Background

### *Physiology and pathophysiology*

The functional role of the lymphatic system can be conceptualized as providing a parallel system of mass transport, thereby supporting homeostasis of the interstitial fluid, and a system of immune trafficking. As a mass transport system, its three functions are: (1) reabsorption of excess interstitial fluid, protein, and waste products; (2) filtration and removal of foreign material from the interstitial fluid; and (3) absorption of lipids from the intestine. To facilitate the function of immune trafficking, lymph nodes are strategically placed within the lymphatic vasculature; they possess the ability to sample the lymphatic fluid, thereby assisting in the immune surveillance of the interstitial space.

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Starling was one of the first to propose that interstitial fluid represents an ultrafiltrate of blood. He hypothesized that lymph production is a function of the opposing forces of capillary hydrostatic pressure, tissue oncotic pressure, interstitial hydrostatic pressure, and plasma oncotic pressure. The first two forces drive filtration while the latter two support absorption. Lymph production reflects the fact that filtration typically exceeds reabsorption by 2–4 liters per day. In addition, net filtration of approximately 100 g of protein from the bloodstream may occur each day. The interstitial fluid also receives waste products including protein and ammonia as well as foreign matter including bacteria and viruses.

The transport of fluid through the lymphatic system is driven by the autocontractile responses of the smooth muscle-invested lymphatic collecting vessels. The impact of extrinsic compressions imparted by the contraction of neighboring skeletal musculature and by the contiguous arteriovenous vasculature adds to a siphoning effect that is imposed upon the thoracic duct by the presence of negative intrathoracic pressure. In the larger vessels, unidirectional fluid movement is facilitated by the presence of an intraluminal valve system, as well as by a two-valve, unidirectional mechanism within the lymphatic capillaries.<sup>6,7</sup> Humoral influences upon flow within the lymphatic system may include various circulating hormones and prostanoids.<sup>8–14</sup>

The presence of edema serves as a nearly universal hallmark of lymphatic vascular insufficiency. The pathological accumulation of tissue fluid in lymphedema ensues from a relative imbalance between the lymphatic load (i.e. the rate of interstitial tissue fluid generation) and the lymphatic vascular transport capacity (i.e. the extent to which disease has functionally or structurally impaired the lymphatic vasculature).<sup>15</sup>

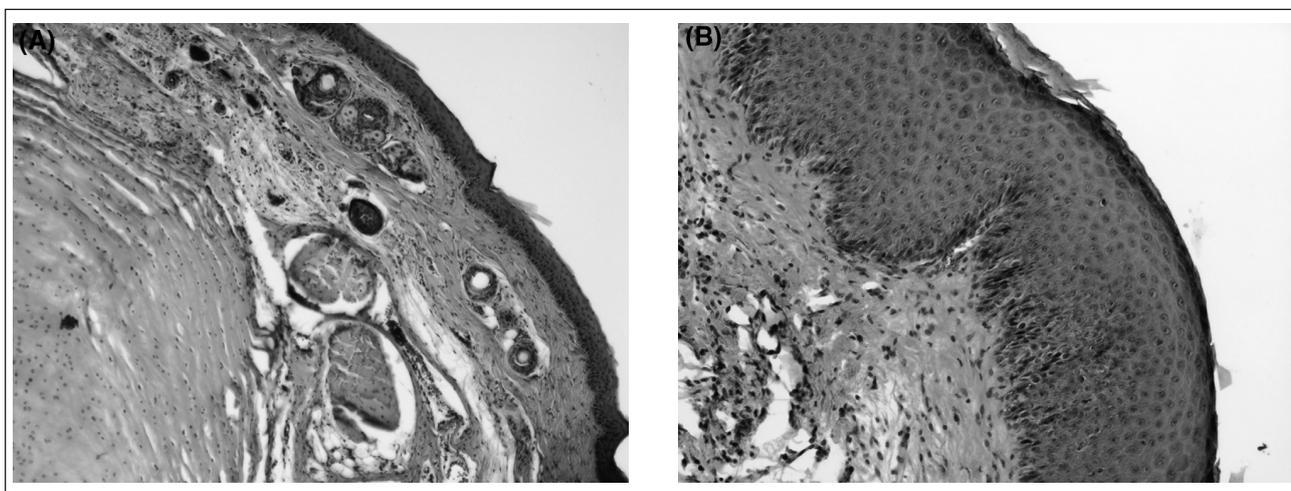
Lymphedema arises when the net entry of fluid into the tissues is positive. Lymphedema occurs commonly both in the context of pure pathological increases in lymphatic load (as would be observed in venous hypertension, for example), of isolated reductions in lymphatic transport capacity

(e.g. as a sequela of lymphadenectomy), and in hybrid pathologies. The implication is that the influx of fluid exceeds the ability of the lymphatic vasculature to remove the fluid. This may occur when the production of lymph increases, when transport by the lymphatics is reduced, or when both changes occur concurrently. Increases in lymph production may arise when Starling forces shift net pressure to favor interstitial fluid production. Increases in venous pressure produce increased hydrostatic pressure within the venous end of the capillary and increase the driving force for ultrafiltration. A decrease in vascular oncotic pressure, such as might be observed in malnutritional hypoproteinemia, cirrhosis, or nephritic syndrome, has a similar effect. Elevated venous pressure occurs in disease states such as right heart failure, deep vein thrombosis, and venous insufficiency. Local inflammation increases capillary permeability, thereby accelerating loss of fluid and plasma proteins to the interstitium. Lymph production may increase 10- to 20-fold in inflammatory states.<sup>16</sup>

### Pathology

In lymphatic vascular insufficiency, the resulting edema can vary from mild to severe, affecting from one or more limbs. Impaired clearance of protein-enriched fluid produces not only edema, but a cascade of pathological alterations in structure and function that typify the tissue response to lymphatic vascular insufficiency.

It is now well-recognized that lymphatic vascular insufficiency predisposes to both a distortion of immune traffic<sup>17,18</sup> and to a loss of normal cutaneous architecture and function.<sup>2</sup> Chronic lymph stasis leads to increased numbers of keratinocytes, fibroblasts, and adipocytes in the integument (Figure 1). Cellular infiltration suggests a chronic inflammatory response.<sup>19</sup> Additional histopathological manifestations of chronic lymphedema include thickening of the lymphatic vascular basement membrane, and fragmentation



**Figure 1.** Cutaneous histopathology in lymphedema. In a murine model of acquired lymphedema, when compared with a normal skin specimen (A), the diseased specimen shows characteristic hypercellularity, which is particularly evident in the dermal–epidermal junction (B).

and degeneration of elastic fibers.<sup>20</sup> Collagen deposition is prominent, ultimately manifesting clinically as cutaneous and subcutaneous fibrosis. These changes are unique to the lymphatic pathogenesis of chronic edema.<sup>21</sup>

In addition, several lines of evidence now suggest that lymphatic vascular dysfunction has a unique and critical influence upon cutaneous adipose biology. Recognition of the nearly universal advent of subcutaneous adipose deposition in the chronically lymphedematous limb has led to the development of directed surgical approaches to remove this deleterious tissue overgrowth.<sup>22–24</sup> The pathogenesis of this lymphatic manifestation remains under investigation. Early clues may be derived from investigations into Prox1 signaling. This nuclear transcription factor plays a critical role in the developmental sequence that leads to lymphatic vascular development.<sup>25,26</sup> While heterozygous functional Prox1 inactivation does not lead to a phenotype of obvious lymphatic dysfunction, impaired Prox1 signaling predisposes to abnormal adipose accumulation and adult-onset obesity, in association with mis-patterned, leaky, and ruptured lymphatic microvasculature.<sup>27</sup>

### Developmental, functional and molecular considerations

The lymphatic vasculature was first described by Aselli centuries ago, and the embryonic origin of the lymphatic structure was proposed in 1902;<sup>28</sup> however, the molecular mechanisms for these mammalian developmental events have only recently been illuminated.<sup>29</sup>

The lymphatic progenitors are believed to reside among the endothelial cells within the nascent embryonic veins. Lymphatic vasculogenesis occurs in four identifiably distinct stages: lymphatic competence, commitment, specification, and vascular coalescence and maturation.<sup>30</sup>

#### Lymphatic competence

Competence is the capacity of cells to respond to an initial inducing signal.<sup>1</sup> The initiating growth factor has not been identified, but all of the endothelial cells of the embryonic cardinal vein have the ability to respond by murine embryonic day 9–9.5.<sup>30</sup> Lymphatic endothelial cell competence can be identified through the cellular expression of two independent, membrane-associated molecular species, lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) and vascular endothelial growth factor receptor-3 (VEGFR-3).<sup>31</sup>

VEGF, a key regulator of endothelial proliferation and migration, is required for vasculogenesis and for physiological and pathological angiogenesis.<sup>32,33</sup> The VEGF family includes five isoforms: VEGF-A, -B, -C, -D, and -E.<sup>34</sup> VEGF-C and VEGF-D and their cognate receptor, VEGFR-3, represent the first and best-studied of the lymphatic-specific signaling mechanisms.<sup>35,36</sup>

With the attainment of vascular maturity, VEGFR-3 expression is largely restricted to the lymphatic endothelium.<sup>25</sup> The primary VEGFR-3 ligands, VEGF-C and VEGF-D, have been well-characterized as pro-lymphangiogenic factors in a number of developmental and postnatal models.<sup>34,36,37</sup> In

conjunction with VEGF-C and VEGF-D, angiopoietin-2 is believed to be responsible for the formation of functionally mature lymphatics following differentiation, through interaction with the Tie2 receptor.<sup>38</sup> Podoplanin is an integral glycoprotein to the plasma membrane of podocytes and colocalizes with VEGFR-3 in early lymphatic structures in a number of tissues.<sup>39</sup>

Although its functional role remains somewhat uncertain, characterization of LYVE-1 as a specific marker of lymphatic development and maturity has been a fundamental advance in the study of lymphatic vascular development and lymphangiogenesis.<sup>40</sup> LYVE-1 is expressed early in the phase of lymphatic competence.<sup>26</sup> With few exceptions, it associates nearly exclusively with lymphatic and lymph node endothelia throughout all developmental stages.<sup>34</sup>

#### Lymphatic commitment

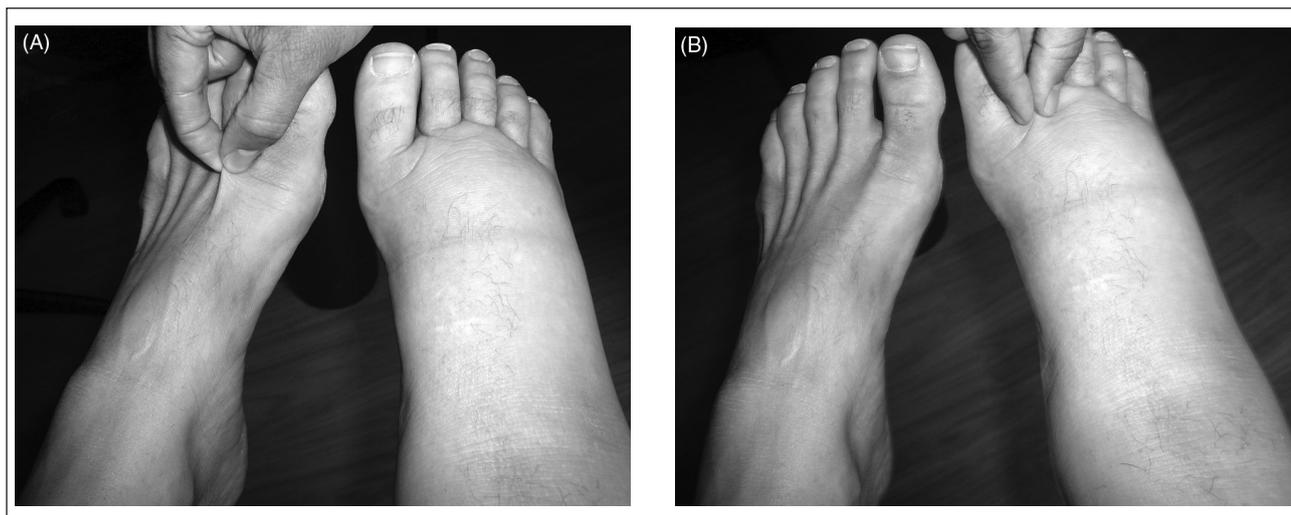
The stepwise differentiation of a specialized lymphatic endothelial cell (LEC) type is initiated by the commitment of a progenitor cell toward an LEC fate.<sup>41</sup> Lymphatic commitment is characterized by the appearance of prospero-related homeobox 1 (Prox1) expression. Prox1 is a nuclear transcription factor whose appearance, unlike LYVE-1 and VEGF-C, is exclusive to cells of committed lymphatic lineage.<sup>26</sup> The Prox1-positive subpopulation of venous endothelial cells orients to one pole of the embryonic cardinal vein and comprises completely the progenitors of future lymphatic vasculature.<sup>25</sup> Prox1 expression shifts commitment of venous endothelial cells from the default blood vascular fate to one of lymphatic lineage.<sup>25</sup>

#### Lymphatic specification, coalescence, and maturation

Lymphatic endothelial cell specification requires the expression of the distinguishing molecular markers that impose the unique phenotype of this cell. As the lymphatic endothelial cells attain a higher level of differentiation, additional lymphatic-specific markers are expressed, with concomitant suppression of blood vascular expression profiles of expression.<sup>25</sup> The committed lymphatic cell population achieves complete autonomy from the local microenvironment of the cardinal vein and migrates peripherally. Budding and migration seed the periphery to prepare for the formation of primary lymph sacs throughout the embryo. Secondary budding and migration characterize the final stage of lymphatic development. The cells form capillaries in a centrifugal fashion, thereby forming the lymphatic vasculature around tissues and organs.<sup>31</sup>

#### Secondary lymphangiogenesis

Many of the molecular events that surround lymphatic vasculogenesis are presumed to play a role in post-natal (secondary) lymphangiogenesis. However, the role of secondary lymphangiogenesis is not well studied outside of the context of tumor biology. Nevertheless, lymphangiogenesis likely occurs along with angiogenesis in the setting of wound healing and inflammation, in a similar transient



**Figure 2.** The presence of Stemmer's sign is considered pathognomic for the presence of lymphedema. In a patient with unilateral lower extremity lymphedema, when compared with the normal limb (A), there is an inability to 'tent' the skin of the lymphedematous interdigital skin fold (B).

fashion.<sup>42,43</sup> There is de novo, budding growth from pre-existing lymphatics that occurs in close proximity to, but separate from, blood vessels.<sup>42</sup>

### Lymphedema diagnosis

Historically, and in clinical terms, the diagnosis and therapy of lymphedema has been based upon the differentiation of primary (hereditary) and secondary (acquired) causes.<sup>28</sup> However, these binary distinctions may not reflect the true clinical spectrum, since primary lymphedema can emerge clinically under the influence of a 'secondary' provoking event, while the predisposition to the development of acquired lymphedema may be, at least in part, genetically pre-determined.<sup>44,45</sup> A corollary phenomenon is the tendency for lymphatic insufficiency to remain clinically silent, or latent, for protracted intervals prior to clinical detectability.<sup>46</sup>

Lymphedema often manifests initially as a mild swelling of the affected limb. At this early time point, pitting edema is almost universally present and elevation of the limb may have a salutary effect upon edema. However, the limb will typically continue to increase in size; as the volume of subcutaneous adipose increases and the tissues become increasingly fibrotic, the pitting nature of the edema can gradually diminish or even disappear entirely.

The clinical diagnosis of lymphedema relies most heavily upon observations made at the bedside. Distinction from other, non-lymphatic forms of edema requires recognition of the unique cutaneous sequelae of lymphedema,<sup>2,5</sup> including peau d'orange and the presence of inelasticity of the skin at the base of the digits, known as the Stemmer sign (Figure 2).<sup>47</sup>

The differential diagnosis of lymphedema includes both chronic venous insufficiency and lipedema. While lymphedema often ensues in long-standing venous insufficiency, the latter does not produce the chronic architectural changes of lymphedema in the skin unless there is a concomitant

secondary impairment in lymphatic function. Early lymphedema shares many features with venous insufficiency, including pitting edema, but stasis ulcers are rarely seen in isolated lymphedema.

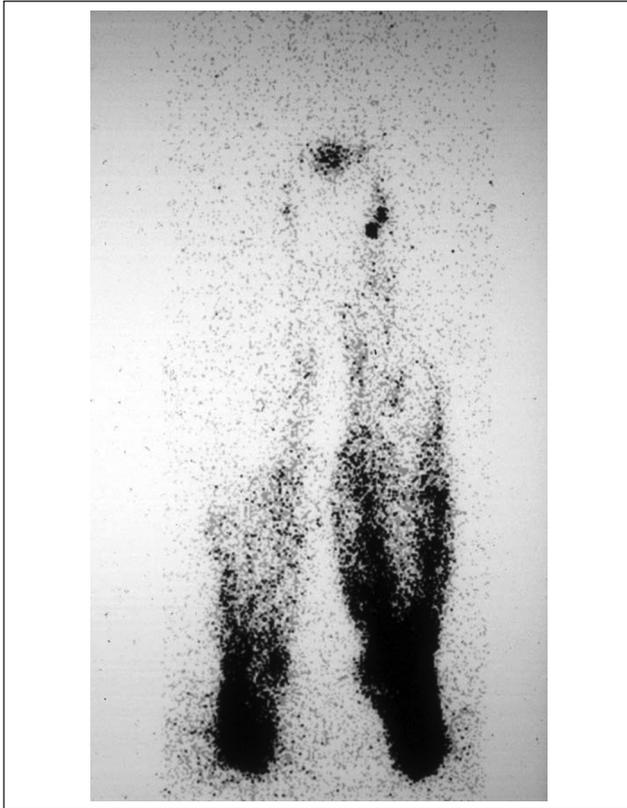
In lipedema, the enlargement of the lower limbs is caused by a pathological accumulation of subcutaneous adipose tissue. The feet are characteristically spared, providing an attribute that readily distinguishes this problem from lymphedema. Patients are almost exclusively female. The typical peri-pubertal onset of lipedema strongly suggests a hormonal pathophysiology, but this has not yet been identified. The presence of lymphatic microaneurysms on pathological specimens distinguishes this condition from simple obesity.

Myxedema can also be considered in the differential diagnosis of lymphedema. This condition arises through the accumulation of hyaluronic acid-rich protein deposits in the affected limbs. It is associated with thyroid disorders and superficially resembles lymphedema. The affected limbs have reduced skin elasticity. Myxedema typically is associated with hypothyroidism, but pretibial myxedema or thyroid dermopathy can occur in thyrotoxicosis.

### Lymphatic imaging

Where necessary, the diagnosis of lymphedema can be confirmed through imaging studies.<sup>48</sup>

Direct contrast lymphangiography has been largely abandoned because of the technical complexity of the procedure and the unacceptable complications.<sup>49</sup> Lymphangiography has been supplanted by indirect radionuclide lymphoscintigraphy, which relies upon the intra- or subcutaneous administration of a radiolabeled large molecule (typically 99m-technetium-labeled sulfur colloid or human serum albumin). The agent is administered parenterally into the interdigital space of the hands or feet. The limbs are serially imaged with a scintigraphic camera. A positive



**Figure 3.** Lymphoscintigraphy in a patient with bilateral lower extremity lymphedema and severe dermal backflow.

study is characterized by absent or delayed filling of the lymphatics and by delayed uptake of the contrast by the proximal draining lymph nodes.<sup>48</sup> Another characteristic finding, dermal backflow, is the imaging equivalent of lymph reflux into the tissues (Figure 3) under the influence of lymphatic hypertension. The intensity of the dermal backflow may carry prognostic significance: in one series of observations, a quantitative grading system for the presence of dermal backflow correlated significantly with the responsiveness of the affected limb to manually applied therapies.<sup>50</sup>

Ultrasonography has little direct utility in the evaluation of lymphedema. Lymph flow cannot be detected by typical ultrasonographic techniques, although it has some application as a semi-quantitative method for assessing tissue fibrosis and edema. Similarly, computed tomography (CT), despite excellent spatial resolution, has limited applicability to the localization of a level of lymphatic obstruction.<sup>51</sup> Qualitatively, CT of the affected limb can be used for its ability to demonstrate a reticular soft-tissue pattern that is characteristic of lymphedema. This reticular pattern can also be demonstrated through T1-weighted magnetic resonance imaging (MRI).<sup>52</sup> More recently, magnetic resonance lymphangiography has been demonstrated to be useful for the direct visualization of lymphatic channels in both primary and secondary lymphedema.<sup>53</sup>

### Emerging diagnostic modalities

Unfortunately, the much-needed circulating biomarkers of lymphatic vascular disease have not yet been identified.<sup>54</sup>

While the ultimate facilitation of early diagnosis and risk stratification will await this discovery,<sup>29</sup> there is an emerging technology, bioimpedance spectroscopy (BIS), that holds great promise for early disease detection. BIS is based on the theory that the magnitude of the opposition to the flow of an electric current (impedance) through a body region is inversely proportional to the volume of fluid in the tissue. In the early stages of lymphedema, with the accumulation of excess interstitial fluid, tissue impedance decreases proportionately.<sup>55</sup> Thus, early diagnosis of lymphedema can be facilitated by comparing measured impedance ratios of normal and at-risk limbs. While alterations in tissue bioimpedance are not limited to lymphatic causes of tissue edema, the instrumentation that permits non-invasive bedside assessment of this physical parameter is increasingly clinically available.<sup>56,57</sup>

The utility of this approach has been demonstrated in early studies. In a cohort of 15 patients with breast cancer-associated lymphedema, bioimpedance spectroscopy favorably correlated with direct limb volume quantitation.<sup>58</sup> When directly compared, the ratios of bioimpedance accurately discriminate lymphedema-affected individuals from healthy controls; in contrast, ratios of measured limb volumes overlap.<sup>59</sup> The predictive efficacy of BIS has also been demonstrated in a cohort of patients scheduled for breast cancer surgery. BIS and arm circumferences were measured pre-operatively and at intervals over the ensuing 24 months. Twenty of the 102 patients developed lymphedema; in each of these, BIS predicted the onset of lymphedema up to 10 months before clinical onset. Estimates of the sensitivity and specificity both approximated 100%. In all but one of the 20 cases, BIS detection antedated the objective detection of edema by circumferential measurements.<sup>60</sup>

### The mandate to treat lymphedema: psychosocial considerations

While lymphedema is rarely, if ever, life-threatening, the advent of this disease carries substantial implications for affected individuals. The impact of lymphedema includes fear surrounding the threat of infection, loss of function and restriction of movement, as well as profound, quantifiable impairment of psychosocial adjustment,<sup>61-63</sup> including the loss of body image and self-esteem, affective disorders, and fear. It has become evident that, in the clinical research performed on lymphedema patients, beyond the assessment of physical modalities, quality of life must be incorporated as an outcome variable.<sup>64</sup>

In breast cancer, the impact of upper extremity lymphedema is often regarded by the patient as worse than the cancer, given the chronic nature of lymphedema. Unfortunately, improvements in surgical and radiotherapy techniques have not substantially impacted the incidence of breast cancer-related lymphedema.

In breast cancer, patients who acquire lymphedema have a higher level of anxiety or depression, a higher likelihood of chronic pain and fatigue, and greater difficulty with social interaction and sexual well-being when compared to lymphedema-free counterparts.<sup>65</sup> In addition, breast cancer

survivors with lymphedema incur higher medical cost and access mental health services to a significantly greater degree.<sup>65</sup> Women who have received surgical and radiation treatment for gynecologic cancers are especially at risk for lower-limb lymphedema, which can have a major impact on appearance, mobility, finances and self-image.<sup>66</sup>

In non-cancer-related lymphedema, health care professionals continue to underestimate disease prevalence by more than 50%.<sup>67</sup> The lower extremities are affected more often in patients with non-cancer-related lymphedema, especially in the context of obesity.

### Treatment considerations

Once detected, the presence of lymphedema mandates very specific modalities of intervention. In contrast to edema that accumulates under the influence of hydrostatic forces (i.e. congestive heart failure, venous hypertension, chronic venous insufficiency), pure lymphatic edema has little meaningful responsiveness to diuretic therapy. This is largely predictable from the Starling forces that govern fluid flux across the blood vascular capillary membrane<sup>68</sup>: while the oncotic pressure of the interstitium is less than that of blood, the use of diuretics, with their impact upon the flux of Na<sup>+</sup> and water, is likely to have only a transient salutary effect, if any, since the retention of macromolecules in the interstitium, the driving force for edema accumulation, is unperturbed. In combined or complex pathologies (lymphatico-venous edema), diuretic therapy may continue to play a meaningful role.

The interventions that comprise complex decongestive physiotherapy (CDPT) have been shown to have salutary short- and long-term effects in lymphedema.<sup>2,69</sup> Efficacy has been demonstrated for each of the components of CDPT, including manual lymphatic massage and multi-layer bandaging. Initially, in a previously untreated patient, compression is accomplished through the repetitive application of short stretch bandaging materials. Each application provides a multilayer compartment surrounding the edematous limb; during muscular activity, the physiological mechanisms that regulate lymphatic contractility and flow are augmented.<sup>70</sup> In addition, during active tissue compression, there is a reduction in the abnormally increased ultrafiltration; this, in turn, leads to improved fluid reabsorption.

Eventually, with repetitive physical interventions and multilayer bandaging, the reduction in volume will achieve a plateau that usually reflects the maximal therapeutic response with aggressive physiotherapeutic interventions. The maintenance phase of therapy is initiated with the introduction and chronic use of elasticized, properly fitted compression garments during non-recumbency. In some patients, nocturnal compression may also be necessary to maintain adequate control.<sup>5</sup> These treatment approaches are time- and labor-intensive, but have been demonstrated to effectively reduce the impact of the disease upon both physical and psychosocial function and quality of life.<sup>69,71,72</sup>

In some cases, the use of adjunctive compressive devices may be deemed desirable.<sup>73</sup> In this context, intermittent pneumatic compression therapy has been shown to augment the

decompressive effects of standard physiotherapies,<sup>70</sup> especially in the context of cancer-associated lymphedema.<sup>69</sup> More recently, an adaptation of intermittent pneumatic compression has been introduced that, while delivering minimal, phasic external compression, endeavors to simulate the effects of manual lymphatic drainage (MLD); the use of such a device, when introduced adjunctively within the maintenance phase of therapy, appears to augment the salutary effects of the standard modalities of CDPT.<sup>74</sup> In this context, a recently published study investigated the role of self-management with a programmable pneumatic compression (the Flexitouch® System) on patients' measured emotional well-being and quality of life. In 155 lymphedema patients (93 with cancer-related lymphedema), pre- and post-treatment assessment with the Short-Form Health Survey SF-12 demonstrated significant improvement in all areas of perceived physical and emotional health.<sup>75</sup>

Historically, the use of intermittent pneumatic compression, particularly in a monotherapeutic fashion, has been hampered by individual reports of complications and lack of efficacy.<sup>76-78</sup> Nevertheless, a physiological basis for the accentuation of flow with the proper use of these devices has been established,<sup>79</sup> and an ameliorative effect on lymphatic protein transport has been demonstrated.<sup>80</sup> The incorporation of intermittent pneumatic compression into a multidisciplinary, therapeutic approach has been advocated,<sup>81-83</sup> but guidelines for both patient- and device-selection remain in evolution. Among the factors to be considered include simple versus advanced devices (the latter offering the options, in various combinations, of multi-chamber design, programmability, and advanced technologies to permit individuated, lymphedema-specific therapeutics). Patient selection factors should determine both the desirability of intermittent compression and the choice of the device to be incorporated into the decongestive regimen: these will include severity of lymphedema; response to conservative therapies; lymphedematous involvement of the trunk, breast, or genitalia; presence of pain or open wounds; heterogeneous, regional variability in the severity of edema; and/or the presence of complications that contraindicate the use of simple, non-programmable devices.

### The future promise of molecular treatment strategies

While there has been a veritable explosion of new molecular insights into lymphatic development and regulation, much still remains to be elucidated. As the diseases of the lymphatic vasculature increasingly benefit from the fruits of biomedical investigation, we can anticipate that translation of mechanistic insights into targeted, rationally conceived therapeutics will become more realistic.<sup>28,29,84</sup>

Increasing investigative attention is being directed toward animal models of lymphatic vascular disease. In addition to the robust models that exist for heritable disorders, such as Milroy's disease,<sup>85</sup> lymphedema-distichiasis syndrome,<sup>86</sup> and other heritable disorders with potential human homology,<sup>87</sup> acquired lymphedema has also been investigated in animal model systems that rely upon the

development of tissue edema following surgical ablation of previously normal lymphatic structures.

The acknowledgment of a unique biology in lymphatic edema is, increasingly, guiding research efforts within this field.<sup>15</sup>

The importance of the lymphatic system is, of course, not limited to lymphedema, but encompasses a broad spectrum of human disease, including neoplastic disease and inflammation.<sup>88</sup> The promise of molecular treatment strategies for the patient with a lymphatic disease will, of course, require the translation of newly derived mechanistic insights into the targeted, rationally conceived therapeutics of the future.

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