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TRENDS IN THE EVALUATION OF LYMPHEDEMA

M.E. Caban

Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas USA

ABSTRACT

This study reviews the criteria and the various measurements available for evaluation of a patient with peripheral lymphedema based on a systematic literature search using Medline. Each clinician needs to be more aware of the measuring technique chosen to determine limb swelling with the inherent limitations of each if errors in calculations or misinterpretations are to be avoided. Determining the patient's symptoms (subjective) and limb changes (objective) are both important for evaluating response to treatment.

There is no gold standard for evaluating lymphedema (1-4). Some have included assessment of clinical changes such as skin folds and texture (5) as equal in importance to the differences in limb volume measurements. Rockson et al (6,7) emphasized the importance of symptoms in early stages of lymphedema. Because untreated lymphedema is progressive (8,9), current practice favors its early identification to initiate treatment with seemingly a better therapeutic outcome (6,10,11).

A basic work up for a patient with chronic arm or leg swelling includes assessment of tumor burden in the lymph nodes, patency of the deep veins and possible soft tissue infection. After exclusion of metastatic cancer, phlebothrombosis and ongoing infection, the diagnosis of "pure" or "uncomplicated" lymphedema rests largely on clinical impression derived from the history and physical examination (12-14) *(Tables 1 and 2)*. Adjunctive diagnostic tests such as ultrasound and isotope lymphography particularly when there is little or no overt swelling or when edema derives from mixed etiology (e.g., both venous and lymphatic) are also useful (15-17).

The study reviews the criteria and types of measurement available for evaluating a patient with peripheral lymphedema. Pertinent physiologic factors as they relate to measurements of lymphedema are also described.

MATERIAL AND METHODS

A systematic literature review using Medline with 1999 Ovid searched for "lymphedema" from 1966 to October 2000 and produced 38,674 articles. Use of the terms explore "lymphedema" and explore "Body Weights and Measures" when combined, excluding "filariasis," yielded 7,965 articles. The search was further limited to "human" and "English," which then yielded 11 articles *(see Table 3)*. The data was then organized to establish the best objective criteria currently available for evaluating a patient with peripheral lymphedema.

Etiology and Pathogenesis

Physiology

An understanding of the pathophysiology of lymphedema is necessary to appreciate the

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TABLE 1
Signs and Symptoms of Limb Lymphedema

Heaviness	Erythema
Tightness	Pain
Hardness	Weakness
Numbness	Seroma
Stiffness	Limitation of motion

TABLE 2
Physical Examination for Evaluating a Swollen Limb

Detectable enlargement of the limb or trunk
Number of skin folds at the axilla, along the limb, digits
Skin color (e.g., erythema; brownish pigmentation)
Skin texture (soft, harden, shiny, taut)
Asymmetric increase in subcutaneous adipose tissue
Pitting edema 0-4
Pulses
Range of motion
Neurologic defects
Measurement of limb volume
Venous collaterals and/or congestion

factors relevant to its measurement. In brief, lymphedema represents an imbalance between lymphatic load and lymphatic transport capability (15,18). Lymphedema is typically progressive (8,9) and exists when the return of lymph flow back to the blood circulation is impaired. With longstanding lymphedema, there is infiltration of chronic inflammatory cells and fibrosis into the regional soft tissue (19).

A normal lymphatic system can handle a modest increase in protein and water load without formation of edema. But factors that greatly increase blood capillary filtration (high-output lymph failure) or impair lymphatic drainage (low-output lymph failure) can alter the lymph formation-lymph absorption equilibrium and result in frank edema (13,15,18). Low output failure of the lymph circulation derives from impaired lymph return or lymph stasis (19). High output failure of the lymphatic circulation exists when lymph flow is increased but, nonetheless, incapable of keeping pace with the increased microcirculatory demand. Examples include ascites associated with portal hypertension secondary to hepatic cirrhosis or peripheral edema from central venous hypertension secondary to congestive heart failure. In either case the Starling microcirculatory forces and lymph dynamics are markedly deranged and edema ensues (20).

Microvascular Factors

Starling demonstrated that microcirculatory forces regulate the partition of extracellular fluid between blood and tissue spaces (18,21-23). These forces nowadays are usually expressed as:

$$J_v = K_{f,c} [(P_c - P_t) - \sigma(\pi_c - \pi_t) = J_L$$

where P_c=capillary hydrostatic pressure, π_c=plasma colloid osmotic pressure, P_t=tissue fluid hydrostatic pressure, π_t=tissue fluid colloid osmotic pressure.

J_v is the net rate of transcapillary fluid movement; $K_{f,c}$ is the capillary filtration coefficient. J_L is the total lymph flow and σ is the osmotic reflection coefficient. Interstitial fluid volume is balanced when $J_v = J_L$. Edema forms when $J_v > J_L$.

Under resting conditions, there is a slight positive net driving hydrostatic pressure across the capillary wall (21). This discrepancy signifies that there is normally a continuous leakage of ultrafiltrate from the blood capillary into the surrounding tissue that becomes tissue fluid. Tissue fluid is gel-like and composed of hyaluronate,

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TABLE 3
Measurement and Diagnostic Criteria of Eleven Articles Searched

Author/Year	Type of study	Criteria	Type of measurement	Limitations
Stanton AWB, et al, 1997 [59]	Comparison of techniques in mannequin, normal, lymphedema arms	Calculates arm/leg volume from a large number of vertical and horizontal diameter measurements as frame moves along the length of the limb.	Perometer	Expensive, errors occur when a cylinder is no longer perpendicular to the light beams. Not accurate for hands (35)
Olszewski W 2000 [66]	Review	Circumference of the ankle/volumeter/Landis method	Perometer/ Landis Circumference	Paper summarizes the use of multiple techniques
Price DA, et al 1993 [67]	Research retrospective (n=47)	Clinical swelling of the feet	Observation	May miss mild edema or therapeutic failure
Harada, et al 1994 [68]	Prospective Research (n=5)	Mean T2, SD or dispersion of T2, STIR, T2 relaxation time	MR imaging	Expensive, difficult to accommodate the limb, results are not immediate
Sitzia J, 1995 [47]	Retrospective	Compare mathematical volume formulae (frustrum is best)	Tape	Need to compare tape measure volumes with imaging actual volumes to determine validity
Mikes DM, et al [64]	Narrative Review	Bioelectrical Impedance Analysis	BIA	Only measures fluid resistance
Roberts CC, et al 1995 [69]	Research	Pinch test of the posterior axillary folds using light pressure springs at relatively constant load-reliable, only method to measure truncal edema	Modified, skinfold calipers	Standard Harpenden skinfold calipers exert pressure of 12.6 gmm-2 - not reliable
Stijns HL, et al 1978 [70]	Case series	Circumference at q 5cm levels	Circumference	Not as accurate as other methods
Calnan JS 1971 [71]	Review	Abnormal superficial lymphatics	Lymphography	Need dynamic lymphatic studies
Guttman FM, et al 1982 [72]	Case presentation (n=2)	Chylous ascites	Abdominal paracentesis	Invasive
Bunce IH, et al 1994 [73]	Prospective (n=25)	Limb volume calculated from circumference	Circumference	Compression of tape prone to error, must record both sides at each time of measurement, water displacement is the only reliable method for irregular shapes (49)

glycosaminoglycans and glycoproteins twisted in collagen fibers that maintain the shape of tissues and organs.

Four major causes of edema include increased blood capillary hydrostatic pressure, decreased plasma protein concentration, increased blood capillary permeability, and blockage of lymph return (24).

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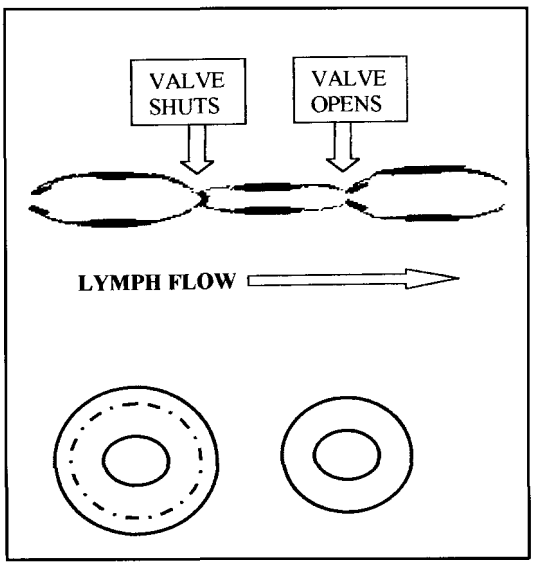

Fig. 1. Upper: Contraction of the lymphangion: the contracted unit (middle) shuts off the inflow valve and leaves open the outflow valve resulting in unidirectional flow. Lower: Cross sectional area of the lymphangion. The middle area contains multiple layers of smooth muscle. The outer side, near the valves, is thinner than the center and contains fewer layers of muscle.

Anatomy

The lymph vascular system is composed of initial lymphatics (superficial) and pre-collector and collector lymphatics (larger and deeper vessels). The initial lymphatics are a subcutaneous blind-ended reticular network formed from lymphatic endothelial cells. There are interendothelial openings that permit the entrance of macromolecules and extracellular fluid through an attenuated basement membrane (25-28). Lymphatic collectors are compartmentalized into pumping subunits (29) termed lymphangions, that contract when there is an increase in intraluminal pressure. With intact lymphatic pathways, multiple lymphangions are connected in series to reach central trunks such as the thoracic duct (15). A lymphangion has a smooth muscle wall and contains an inflow valve that moves fluid to an outflow valve to insure unidirectional segmental flow *(Fig. 1)*. Földi et al has described mechanical receptors or stretch-sensitive pacemakers in the lymphangion that respond to increased intralymphatic pressure (18). Lymphatic capillaries can adjust their shape and size to changes in the interstitium. Lymphatics lack a basement membrane altogether or have an attenuated one (27,30). The initial lymphatics or capillaries are porous such that protein and macromolecules can readily enter them from the interstitium.

Lymph fluid starts at the initial lymphatics, and drains into pre-collector and collector vessels that eventually empty into regional nodes (25). After passage through one or more lymph nodes, lymph drains into postnodal collectors that fuse to form larger lymphatic trunks, which, in turn, drain into central lymph ducts. The thoracic duct is the largest lymphatic and terminates at the angle between the left subclavian and internal jugular veins. In this way, lymph originates from the interstitium from blood capillary filtrate and returns to the bloodstream to maintain overall fluid balance.

Characteristics of Interstitial Fluid-Protein Concentration

Bates et al (22,31) questioned the premise that with lymph stasis edema fluid is invariably high in protein content in patients who have undergone treatment for breast cancer. Thus, the protein concentration of interstitial fluid in an edematous arm when compared with the contralateral arm, yielded a slightly lower protein concentration. The interstitial hydrostatic pressure in the edematous arm was also increased. They concluded that there was a negative correlation between the interstitial fluid protein concentration and the volume of the arm (31).

Blood Vascular Factors — Causal or Contributors to Edema

There are several reports of concomitant blood vascular abnormalities in peripheral

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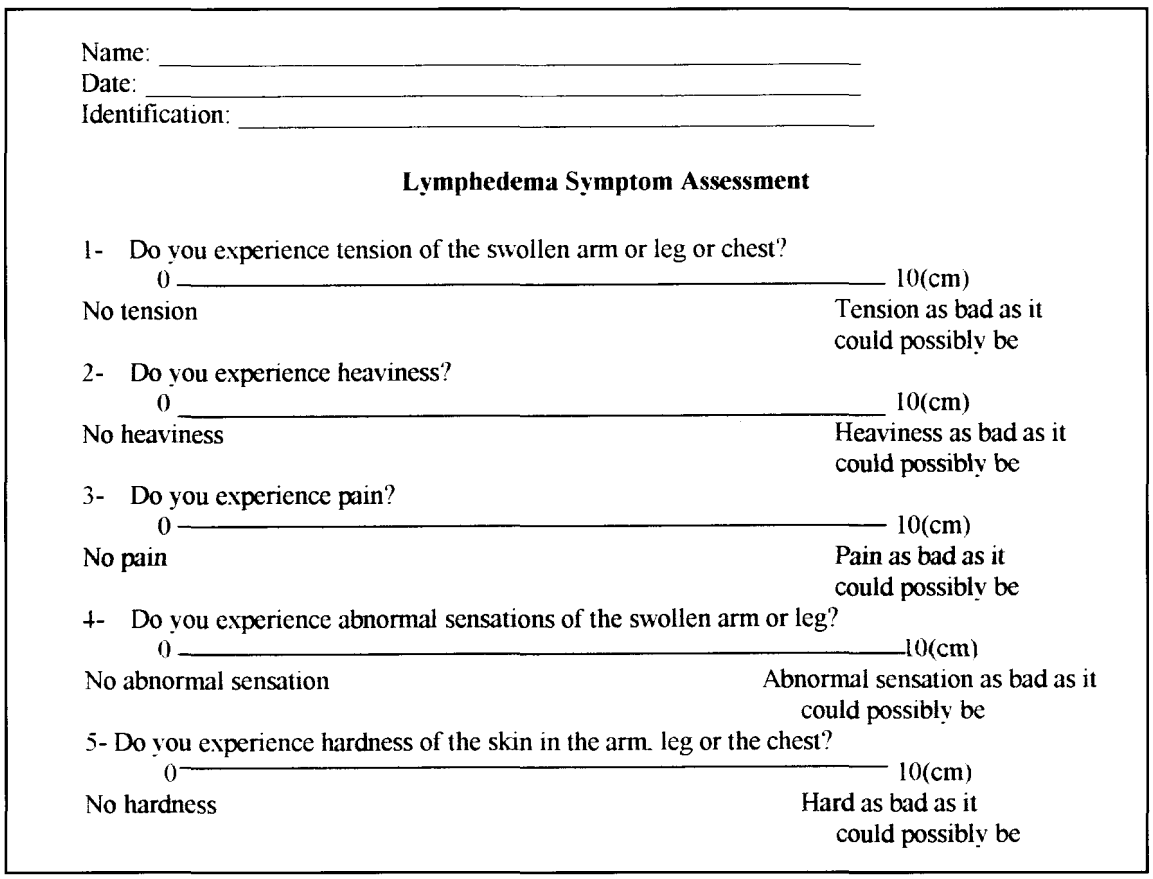

Fig. 2. Visual analog scale for evaluating of subjective symptoms of lymphedema.

lymphedema. Svensson et al (32,33) challenged whether lymph stasis alone with high lymphatic obstruction is the sole cause of edema. Using ultrasound examination in the axillo-subclavian venous systems of 81 patients, he observed thrombosis, narrowing or lack of axillary and/or subclavian veins. Other workers (34) have related examples where axillary vein stenting and percutaneous venoplasty reduced swelling in patients with unilateral arm edema after treatment for breast cancer. Rockson and Szuba (6) also described a patient with unilateral lower extremity edema from chronic ipsilateral iliac vein compressed by the contralateral iliac artery. Whereas percutaneous balloon venoplasty and stenting resolved the venous blockage, secondary lymphedema subsequently ensued. Kim et al (35) demonstrated that functional impairment of the venous return can aggravate lymphedema.

The role of blood vascular factors in postmastectomy arm edema was further questioned when Stanton et al measured blood flow in edematous and normal arms using venous occlusion plethysmography and an optoelectronic volumeter (Perometer) (36). They reported reduced blood flow in the arm of postmastectomy edema suggesting that hyperdynamic blood flow was not a contributor to arm edema after treatment of breast cancer.

CLINICAL MANIFESTATIONS

Postoperative swelling after operative

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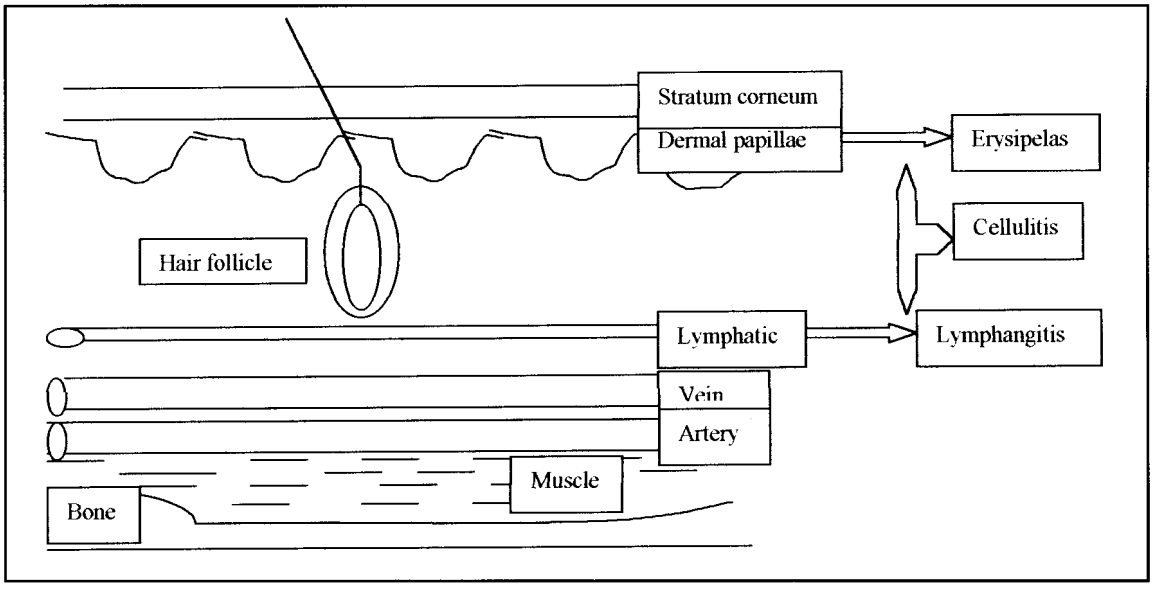

Fig 3. Diagram showing the skin layers affected in various soft tissue infections.

treatment for cancer is typically transitory. Most often it responds to limb elevation and gentle muscle pumping exercises (6,37). A subgroup of patients, however, progress to full-blown lymphedema (38). Piller has described a latent phase during which a number of physiological events occur without development of overt lymphedema. This latent phase may precede frank lymphedema for several months or years (11,39,40). Lymphocytes and macrophages infiltrate the soft tissue even in the early stages of lymphatic failure (38). Activation of the macrophage likely initiates a progressive inflammatory process (8,9), and stagnant plasma proteins may be the inciting factor. Tissue proteins that stagnate increase interstitial osmotic pressure and thereby aggravate the accumulation of edema fluid. Ultimately, deposition of collagen results in skin fibrosis (19,38).

Subjective symptoms even without overt edema are frequent in early lymphedema. These symptoms *(see Table 1)* can be monitored and serially followed. A Lymphedema Symptom Assessment sheet (41) is an example of a visual analog scale that the patient can fill out during the baseline visit and during follow up *(Fig. 2)*. Johansson and colleagues described a similar protocol to measure pain, heaviness and tension (9,42). Swedborg et al utilized the Borg scale, an eight-degree rating, to quantify symptoms experienced by lymphedema patients (33). A careful physical examination, however, usually establishes the diagnosis (17) *(see Table 3)*.

Malignant lymphedema refers to peripheral swelling caused by tumor cells infiltrating draining lymph nodes or by tumor bulk directly compressing and/or invading lymphatics (18,37,43-45). Sustained reduction of swelling is rare in these patients even when treated by manual lymph drainage (18). Földi et al reported that in a group of 21 such patients, 52% did not maintain limb swelling reduction after 3 years. Patients with benign lymphedema (n=399), on the other hand, demonstrated substantial volume reduction with manual lymphatic drainage (18). Three complications of lymphedema that require prompt antibiotic treatment are: *(Fig. 3)*

1. Cellulitis or an acute localized inflammation of the deep subcutaneous

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tissues and sometimes muscle compartment associated with edema. The most common causative microorganism is group A Streptococcus (46).

2. Erysipelas, an acute, superficial form of cellulitis involving the dermal papillae caused by Streptococcus group A and characterized by hot, bright red, edematous, well defined margins with a raised indurated border. Pain, fever and intense red color are present, but typically resolve once proper antibiotic drugs are initiated.

3. Lymphangitis is characterized by painful, red streaks along skin lymphatics. The most common causative microorganism is also beta hemolytic Streptococcus. Repeated episodes of cellulitis, erysipelas, or lymphangitis tends to worsen lymphedema (30).

Measurement of Lymphedema

Whereas there is no accepted method that is sensitive and specific enough to screen all patients with limb swelling (1), the easiest way to assess limb asymmetry is by use of circumferential measurements. Tape measurement is simple and inexpensive and can be readily converted into a volume determination using the formula of a frustum or a truncated cone (47). Water displacement is also a good method especially in measuring an irregularly shaped limb (5,48,49). An electronic tonometer has the advantage of measuring tissue compliance and the degree of compression (5,50,51). It avoids the false impression that decreased limb circumference results from improvement of edema as opposed to fibrosis. Ultrasonography is the technique most often used to evaluate venous patency and valvular competence (15,52). Doppler ultrasound can also provide information on skin thickness (35). Venous abnormalities have been reported with variable frequency in an edematous arm (32,34,53). Bourgeois et al (52) studied venous abnormalities using radiological phlebography in 25 patients with lymphedema and reported 20/25 with venous abnormalities and 2/25 with axillary vein thrombosis. Pecking et al (54) reported venous abnormalities in 18 of 75 patients (24%) suspected of lymphedema. Others authors describe lymphedema "activation" or worsening in the presence of venous abnormalities.

A sensitive diagnostic test to examine lymphatic abnormalities is lymphoscintigraphy and it has been used to evaluate for therapy (54,55). Lymphoscintigraphy is a simple technique that involves injection of colloidal radioactive tracer intradermally into the webspace between the fingers or toes (17,52). Lymphatic tracer uptake is depicted using a gamma camera and computerized display scintiscanner to follow lymph transport and lymph nodal uptake. Lymphoscintigraphy and direct lymphangiography have been used to assess primary lymphedema. Lymphoscintigraphy is more commonly used nowadays because it is minimally invasive, safe and can be easily repeated (13,17,24,56); however, it is only semi-quantitative (57). Svensson et al (58) recently compared 99m Tc labeled poyclonal immunoglobulin (HIG) with 99m-Tc labeled human serum albumin (HSA) to measure lymph flow in subjects undergoing lymphoscintigraphy. He concluded HIG was a potentially useful agent when injected into the web spaces but less so at the forearm level. In this study, clearance rate measurements were not significantly different between the lymphedematous and the contralateral normal arm.

Computerized limb volume measurement system (CLEMS) measures shape and volume. The device consists of a mechanical arm (optical encoders), digitizer and a personal computer (48). A similar design involves the Perometer or optoelectronic volumeter (59,60). CLEMS consists of a sweeping frame that contains rows of infrared light that computes volume from a large number of vertical and horizontal diameter measurements and provides measurement of the circumference, contour and cross sectional area of the limb. Potential sources of

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error are if the beam lights are not perpendicular to the limb or if the shape of the limb differs considerably from a circle or ellipse. The Perometer is generally reliable and fast. Magnetic Resonance Imaging (MRI) provides more precise anatomical information. A honeycomb pattern with thickening of skin characterizes the edema which is typically localized to the epifascial compartment. Venous edema, in contrast, often involves fluid trapping in both the epifascial and subfascial compartments. MRI also can identify enlarged lymph trunks and various causes of lymphatic obstruction (e.g., intraabdominal cancer). On occasion, MRI complements other information for corroborating the diagnosis of lymphedema. In short, MRI can semiquantitate the degree of fat, and liquid in the affected limb when compared with the non-affected limb. A drawback of MRI is the relative lengthy time needed for scanning and the limited ability to accommodate a markedly swollen limb (17,61). Computed tomography (CT) provides cross-sectional imaging and displays the density of the subcutaneous and muscle compartments (62,63), but it is not a useful screening method. Both MRI and CT are costly and are used as adjunctive diagnostic tools. Mikes et al (64) propose the use of bioelectrical impedance analysis (BIA) to measure total limb volume. Essentially, the change in impedance, that is, the effective measure of conductivity, accurately quantifies accumulation of edema fluid. Three basic components of a limb are bone, muscle and electrolytic fluid (lymph and blood). By assuming that no major changes occur in bone, muscle or blood in a lymphedematous limb, an altered BIA corresponds to changes in fluid volume (i.e., edema) of the affected compared with the non-affected limb. The BIA is a promising technique because it detects early edema changes and because it is quick and inexpensive, it offers quantification of limb fluid gain or loss. On the other hand, BIA primarily quantifies changes in fluid resistance (64); it does not measure skin thickness or tissue fibrosis and impedance measurements may be factitiously affected by skin temperature. Moreover, tissue fluid accumulation may occur with pregnancy or menstruation and with altered electrolyte balance as in malnourished states such as diabetes mellitus. In short, BIA should be cautiously interpreted when applied to lymphedema patients because it measures primarily changes in fluid resistance only.

DISCUSSION

Consistent guidelines are needed for the evaluation of the patient with lymphedema. A comprehensive history and physical examination are still key factors in the proper diagnosis of lymphedema (13). Limb volume measurements allow objective follow up of the progression or reduction of edema. Ramos et al (3) suggest after a review of 69 patients with arm lymphedema after breast cancer therapy that the time of onset of lymphedema is of lesser importance than the limb volume difference, when the arm swelling occurred soon after or years later. Others, however, have proposed skin texture as more reliable than waiting for differences in limb volume to occur in terms of prognosis. Thus, Clodius et al (5) observed that a small limb circumference and harder skin indicated ongoing subcutaneous fibrosis rather than a favorable response to non-operative compression treatment. Perhaps incorporating determination of the subjective symptoms using a visual analog scale *(see Fig. 2)* may help in the early detection of lymphedema.

The absence of a measured volume difference in a limb suspected of lymphedema should not detain non-operative intervention or follow-up of the patient closely (43). Early recognition of limb lymphedema and prompt initiation of compression treatment promotes a better outcome. Failure to respond to non-operative therapy may indicate a concomitant blood vascular abnormality (7,34) or other co-morbid conditions (30).

Table 2 examines the criteria and types of

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measurement frequently used to evaluate for lymphedema. Although each technique has its advantages and drawbacks, whichever one is chosen should be used consistently to determine reliably treatment success or failure. Whereas, the criteria to evaluate a patient with lymphedema is largely based on the history and clinical examination, decreased limb volume alone is by itself a potentially false indicator of successful edema reduction because it may occur with progressive soft tissue fibrosis. Both improved symptoms (subjective) and documented limb volume reduction (objective) are together the best indicators of treatment success or failure.

Areas for Research

Many basic questions remain unanswered in regards to lymphedema. There is a need to identify a reliable marker (anatomic, physiologic or biochemical) to provide a clearer prognosis when evaluating such a patient. Drug options are still severely limited for patients with primary or secondary lymphedema whether after treatment for malignancy or as a manifestation of persistent cancer. The identification of cytokines released by tissue macrophages and their inactivation may direct clinical trials in the future. Considerable research is still needed, however, to identify better treatment options and prognostic factors in this disorder.

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Mabel E. Caban, MD
Dept. Physical Medicine and Rehabilitation
Baylor College of Medicine
2506 Gramercy St.
Houston, TX 77030
Telephone: 713-669-1807
Fax: 713-669-1816
Email: mcaban@bcm.tmc.edu

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