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IUA-ISVI CONSENSUS FOR DIAGNOSIS GUIDELINE OF CHRONIC LYMPHEDEMA OF THE LIMBS

B.-B. LEE, P.L. ANTIGNANI, T.A. BARONCELLI, F.M. BOCCARDO, H. BRORSON, C. CAMPISI, R.J. DAMSTRA, M. FLOUR, A. GIANNOUKAS, J. LAREDO, N.F. LIU, S. MICHELINI, N. PILLER, S.G. ROCKSON, A. SCUDERI, G. SZOLNOKY, T. YAMAMOTO

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Lee BB, Antignani PL, Baroncelli TA, Boccardo FM, Brorson H, Campisi C, Damstra RJ, Flour M, Giannoukas A, Laredo J, Liu NF, Michelini S, Piller N, Rockson SG, Scuderi A, Szolnoky G, Yamamoto, T

Corresponding Author:
Byung-Boong (B.B.) Lee, M.D., PhD, F.A.C.S.
Professor of Surgery & Director, Center for Lymphedema and Vascular Malformation, George Washington University School of Medicine
Address: Division of Vascular Surgery, Department of Surgery, George Washington University Medical Center, 22nd and I Street, NW, 6th Floor, Washington, DC 20037 USA

Mieke Flour, MD
Dermatology Department, Vascular Centre,Multidisciplinary Diabetic Foot Clinic
University Hospital Leuven, Leuven, Belgium

Athanasios D. Giannoukas, M.Sc., M.D., PhD, FEBVS
Professor and Chairman, Department of Vascular Surgery, University of Thessaly, School of Health Sciences, Larissa, Greece

James Laredo, MD, FACS
Associate Professor of Surgery, Co-Director, Center for Lymphedema and Vascular Malformation, Division of Vascular Surgery, Department of Surgery, George Washington University School of Medicine, WashingtonWashington DC, USA

Ning-fei Liu, MD ，Ph.D
Professor of plastic surgery and Director of lymphology center, Department of Plastic & Reconstructive Surgery, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Stanley Rockson, MD
Allan and Tina Neill Professor of Lymphatic Research and Medicine, Director of the Stanford Center for Lymphatic and Venous Disorders, Chief of Consultative Cardiology, Stanford University School of Medicine, Stanford, CA, USA

Sandro Michelini, MD
President of the European Society of Lymphology. Chief of Department of Vascular Rehabilitation, San Giovanni Battista Hospital, Rome, Italy

Angelo Scuderi, MD
Santa Lucinda Hospital (Sorocaba – Brazil) – Pontificial Catholic University os Sao Paulo. Brazil.
President of UIP (2011-2015)

Gyozo Szolnoky, MD, PhD
Assistant Professor, Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

Neil Piller, PhD , FACP
Professor of Lymphology, Advanced Studies Coordinator, MD program, Director of the International Lymphoedema Framework and the Lymphoedema Research Unit, Department of Surgery, School of Medicine Flinders University and Flinders Medical Centre, Adelaide, South Australia

Takumi **Yamamoto, MD**
Assistant Professor, Department of Plastic and Reconstructive Surgery, the University of Tokyo, Tokyo, Japan

Prologue

It has been a tremendous challenge from the outset to organize a diagnosis guideline for chronic lymphedema by IUA (International Union of Angiology) and ISVI (Italian Society of Vascular Investigation) as a joint project. Despite such enthusiasm shared by a few leading members of two different societies who initiated this task sharing same goal, they soon encountered many obstacles to proceed with significant limitation (e.g. lack of sufficient data/evidence to draw the conclusion/consensus). But they determined to provide a guideline for contemporary diagnosis of chronic lymphedema, the most crucial part of its management; with relentless efforts they expanded their boundary to reach out many outstanding world authorities in various issues of lymphology to meet its mandate to fulfill its role.

They did spare no pain to collect all of the currently available consensus documents, many national and international, to lay proper ground to review as references. Based on the principle of evidence-based medicine, every inch of current knowledge in the diagnosis field of limb swelling was reassessed to draw the consensus, from initial interview for history taking and physical examination to newly introduced a variety of tests based on new technology to differentiate with other etiologies of lower limb edema. Indeed, many world renowned physicians specialized in lymphology collaborated decisively to organize this important document for proper orientation for the clinicians when facing the cases of lymphedema in a remarkable way.

It has been a special privilege for me to participate to this unique IUA-ISVI consensus and assist them to complete successfully under the auspices of UIP (International Union of Phlebology) to maximize its role among not only the angiologists but also phlebologists throughout the world.

Finally, I want to congratulate Drs. BB Lee and PL Antignani leading this enormous task to complete successfully with rest of authors/members, which will remain crucial contribution in this unique field of lymphology.

Angelo Scuderi, MD
President of UIP

Abstract

The current document is intended to define a consensus on the diagnostic guidelines for patients with lymphedema, based upon literature-based evidence, both clinical and investigative. General diagnostic guidelines include systemic evaluation; assessment of venous function; duplex ultrasonography; and lymphoscintigraphy.
Proper diagnosis should allow appropriate clinical and laboratory staging of the disease for the assessment of progression of the condition and its response to treatment. Diagnosis should include an assessment of the infections in the early and latent stages.
Lymphedema is assessed by the stage of disease (0-III) and WHO guidelines for International Classification of Functioning, Disability and Health and Quality of Life issues can be used as a reference for the impact of this complex condition on social, emotional, and physical function. It is the authors' intent that this document stimulate further inquiry and discussion regarding all aspects of lymphedema diagnosis.

Key words: Chronic lymphedema, Clinical staging, Duplex ultrasonography, Volumetry, Tissue Tonometry, Bio-impedance Spectroscopy, Radionuclide lymphoscintigraphy, CT, MRI/MR lymphangiography, Indocyanine Green Lymphangiography, Direct/Indirect lymphography, Molecular diagnosis

Introduction

The management of chronic lymphedema remains a challenge for patients and clinicians worldwide despite the progress over the past several decades which has been significant, both in the diagnosis of, and therapy for, this disabling condition.[1-3]

Therefore, as a joint project, the International Union of Angiology (IUA) and the Italian Society for Vascular Investigation (ISVI) under the auspices of the International Union of Phlebology (IUP) invited an expert multidisciplinary panel to convene and arrive at a consensus on the guidelines for physicians on the diagnostic evaluation of chronic lymphedema.

This document presents contemporary concepts encompassing a broad range of new and old diagnostic modalities. We respect all of the currently available consensus documents, previously prepared by the many national and international societies. We also strongly encourage the review of these expert documents as additional references in addition to this consensus document.[1-5]

This document is not meant to overburden the individual, local or national medical communities with specific recommendations, as these may be impractical to some where there is limited availability and access to the recommended technology. On the other hand, we hope that those with experience, knowledge and expertise beyond that described in this document will continue to offer their input to this living consensus document.[1, 2]

The aim of this Panel is therefore, to define a consensus on the diagnostic guidelines for patients with lymphedema based on the evidence found through clinical and instrumental investigations in the literature with appropriate comparison and experiences. But, the level of evidence of many of the clinical studies on the results of the various lymphedema treatments today is still very low. Appropriate 'multicenter' studies will be mandatory to provide a common ground of precise, reliable and reproducible/repeatable measurements for the appropriate comparison of the management outcome among various lymphedema centers.

A precise and reproducible method for measurement of the dimensions of the limb affected by lymphedema, for example, is mandated as the first step to define the degree/extent of the lymphedema and monitor its natural progression and also the results of the various treatment modalities (medical, physical, surgical).

Recommendations in the document are graded according to scientific evidence. The panel adopted the system used by Guyatt et al [6-8], and the document has two grades of recommendations: Grade 1 (strong) recommendation, which is reserved for those tests, where the benefits clearly outweigh the associated risks and Grade 2 (weak) recommendation, which is reserved for those diagnostic tests, where the benefits do not significantly outweigh the associated risks. The quality of evidence can be high (A), moderate (B), low or very low (C) (Appendix- Table 1)

Diagnostic Evaluation

General Guidelines

As the first step of the diagnostic procedure, systemic causes of limb swelling/edema: e.g. heart and

liver failure, kidney disease, hypoproteinemia, pulmonary hypertension, hypothyroidism, cyclic edema, medication side effects (calcium channel blockers, steroids, NSAID, several chemoteherapeutic drugs) should be ruled out properly. In addition to a complete history and physical examination, some additional tests should be ordered when the lymphoscintigraphy alone is insufficient to make a full diagnosis of lymphedema/lymphatic dysfunction. [9-12]

As the second step of diagnostic evaluation, the venous origin of limb edema should be ruled out since the venous and lymphatic systems are closely interdependent and their dysfunction often co-exists indicating the close relationship between venous and lymphatic development. [11-13] Thus, venous and lymphatic systems should always be evaluated together when investigating chronic edema.

Duplex ultrasonography therefore should be included with lymphoscintigraphy in all forms of lymphedema including congenital, for differentiation from edema of mixed etiology.[1, 2, 14] In some genetic forms of primary lymphedema such as Milroy disease and lymphedema distichiasis syndrome, venous valvular dysfunction (venous reflux) frequently co-exists [13]

Proper diagnosis should allow appropriate clinical and laboratory staging[15-17] of the disease for the assessment of progression of the condition and its response to treatment. Diagnosis should include an assessment of the infections in the early and latent stages; such evaluation should be repeated aggressively not only for timely treatment but also for effective prevention of various conditions such as tinea pedis. [1, 2]

Diagnostic evaluation should include appropriate assessment of patient compliance, as the outcome of successful management is totally dependent on this crucial factor. [1, 2]

Lymphedema among children is chiefly of primary origin. Their lymphedema can be part of a syndrome if there are other concomitant phenotypic abnormalities and if a genetic defect is recognizable. However, recognition relies upon careful personal and family history and physical examination in the initial phases. [1, 2]

Clinical evaluation will not be complete without documentation for lymphedema stage, [3-5, 15-18] including Stage 0 through Stage III, classification of severity of edema (volume): Mild – Moderate – Severe, proper description of the skin and subcutaneous tissue changes, and functional assessment of limb affected by lymphedema. WHO guidelines for International Classification of Functioning, Disability and Health and Quality of Life issues can be used as a reference for the impact of this complex condition on social, emotional, and physical function.[19-21]

Clinical Evaluation

Evaluation of patients must include a detailed history and clinical evaluation along with a thorough physical examination.[1,2] History should include age at onset, travel to tropical countries and history of all causes that could result in secondary lymphedema including the medications with edema-causing potential (e.g. antipsychotics, anti-parkinsonian, cyto-toxics, bisphonates, antihypertensive). History of temporary edema of the affected limb or other areas must be noted and a detailed family history of limb swelling should also be recorded.

Signs and symptoms should be recorded. These include non-pitting edema, skin changes such as *peau d'orange*, pinkish-red skin discoloration, hyperkeratosis, dermatitis, eczema, ulceration, varicosity, lymph vesicles, drainage of fluid, clear or milky, or yellow discoloration or other abnormalities of the nails. The presence of Stemmer sign[22] (skin fold of toes or fingers can barely be

lifted), squaring of the toes, or puffiness of the forefoot (buffalo hump) should be noted. Such conditions/findings should be documented with appropriate clinical photos taken. Severity of pain (by using a visual analogue pain scale) and disability (by using a quality of life questionnaire) documentation at baseline is important to classify disease burden for each patient and in order to evaluate the effectiveness of any treatment.

When the lymphedema is primary, as a clinical manifestation of truncular lymphatic malformation[23, 24], the presence of venous, arteriovenous, or capillary malformations [25-27], or any tissue overgrowth (eg increased/decreased leg length[28, 29]), or increase in fat or muscle bulk should be recorded. Finally, any complications, such as cellulitis, lymphangitis, malnutrition, immunodeficiency or, rarely, suspicion for malignancies (lymphangiosarcoma) must be documented. [1, 2]

Diagnostic Tests - General Principles

An appropriate combination of non- to minimally-invasive tests should typically be able to provide all of the information necessary to insure an adequate diagnosis and lead to the correct multidisciplinary, targeted, and sequenced treatment strategy. The tests and the information they can provide are indicated below.

Non-invasive evaluations[30-34]

- Basic/Essential Tests
- Volumetry[35]: Measuring the Dimension of the Limb
    - Water measurement (plethysmography)
    - Circumference measurements according to Kuhnke
    - Optoelectronic volumetry
    - Automatic digital measurement
- Radionuclide Lymphoscintigraphy[32-34, 36]
- Duplex ultrasonography [1, 2, 13, 37]
    - Ultrasound of soft tissues
    - Echo Color Doppler
- MRI with/without contrast [38-40]
- MR lymphangiography[41, 42]
- CT scan [30, 31]

- Optional Tests [43, 44]
- Tissue Tonometry
- Bio-impedance Spectroscopy: Bioimpedence Analysis (BIA)[45]
- Indocyanine Green (ICG) Lymphangiography[46, 47]
- Microscopic fluorescent lymphangiography [8, 49]
- Whole body blood pool scintigraphy (WBBPS) [50]
- Air plethysmography[51]
- Plain X ray
- DXA (Dual Emission X-ray absorptiometry) [52, 53]
- Ultrasonographic lymphangiography [54]
- Moisturemeter (tissue dielectric constant, TDC) [55]

Invasive evaluations

'Invasive' tests are seldom needed for the actual diagnosis but are occasionally needed for

differential diagnosis.
Further studies with invasive tests such as direct puncture percutaneous lymphangiography can be generally deferred to later stages if there is need for refining the diagnosis or if surgical or other invasive therapeutic measures are considered. Otherwise, these should be reserved for road-mapping in subsequent therapy if needed.

On some occasions an invasive study is required to provide more information for an accurate differential diagnosis. These tests and the information they provide are indicated below;

- Direct oil contrast (ascending) lymphangiography/lymphography[56-58]
- Indirect lymphography[59, 60] using water soluble contrast agents
- Direct puncture percutaneous lymphangiography [1, 2, 61]
- Fine needle aspiration biopsy of lymph node
- Skin biopsy in cases of suspected sarcoma, skin cancer or differential diagnosis of warty lesions

Volumetry: Measuring the Dimension of the Limb

A precise and repeatable measurement of the dimensions of the limb affected by lymphedema is needed in order to define the degree of the lymphedema and monitor its development at the same time, with regard to the natural progression of the pathology and the results of the various treatment modalities (medical, physical, surgical). The distance from certain anatomical sites of the limb (ankle, knee) should be recorded. [62-70]

A review of the literature revealed that among 43 clinical trials for the evaluation of the effectiveness of peripheral lymphedema treatment, 14 (42%) took only the circumference measurement in centimeters to compare with those at pre-defined points or as a sum of circumferences, whereas 19 (58%) evaluated the change of volume of the limb utilizing a direct or indirect methodology).

In the case of unilateral lymphedema, after calculating the volume of the two limbs, the volume regarding the suffering limb must be calculated with respect to the healthy limb and the volume of the edema (excess volume). But for bilateral edema, it is necessary to compare each limb with itself over time, as it is not possible to use the contralateral limb as a control.
In the case of surgical operations with lymphadenectomy, it is advisable to take pre-operative measurements of the limbs as reference for calculating the volume of any secondary lymphedema.

Water measurement of limb volumes [71]
A recent study showed a coefficient of variation (CV%) of 0.609% when using plethysmorgaphy. The circumference measurement also correlates well with the outcome of water replacement and is easier to use, as it does not need the plethysmography devices, which may not always be available.[62]

Water replacing plethysmography can be used for separate measuring the volume of the hand or foot with fewer problems than that of the entire limb.[72]

However, the logistical difficulties associated with water displacement may make it difficult to use routinely in clinical practice. Inverse water volumetry may be a good alternative because of its greater amenability. However, this method is applicable only to the upper extremity. A drawback is that it does not measure the upper half of the upper arm. However, it represents an improvement upon the classic method of water displacement volumetry. This method is a new gold standard and commercially available in Europe. Available for arm volume measurements, it has very high precision.

The Panel considers water volumetry is the gold standard but careful tape measurements are a faster and less expensive alternative provided one acknowledges their limitations in accuracy. However, the Panel recommends that volume measurement with water is undertaken for measuring the volume of the hand or foot, or for scientific research purpose, where it is necessary to measure the absolute volume of the limb for comparisons with other measurement techniques.
[Strength of recommendation:1 (strong), Quality of evidence:C (low) [6-8]]

Measurement with measuring tape [73]
The volume of the limb can be indirectly calculated with a precise measurement of the circumferences of the limb at various levels using a tape. Compared to direct measurements, this measurement has the advantage of generating low cost, widespread availability and ease of performance. However, the operator's accuracy in reading the measurement is essential. In order to guarantee reproducibility of the measurement, it is necessary to identify all the various measurement points with certainty.

In addition, there is uncertainty about the optimal limb position for accurate garment fitting, in order to provide the desired pressure gradient in a comfortable garment. Should limb measurement be performed in the horizontal or vertical position? Because, circumferences are sensitive to position, due to fluid movements and tissue flaccidity, this can perhaps produce a garment that is not totally appropriate or comfortable to the patient. [73]

Nevertheless, typically circumferences are measured from the wrist/ankle every 4 cm the the most proximal point, according to Kuhnke Each volume segment is measured according to the formula of a truncated cone. The segments are then summed to get the arm/leg volume. It is important that the normal contralateral arm/leg is used as the reference when calculating the excess volume. This method does not include the hand volume because the hand is oval in shape, and the formula for the truncated cone cannot be used.

The tape measure has to be flexible and not too long in order to stay in close contact with the skin. Even the smallest amount of traction must be avoided so as not to compress the tissues and underestimate the limb size. A standardized tape measure (with small weights attached to it) and measurement technique have been developed to overcome these practical difficulties. [74]

Measuring the volume with the tape technique has demonstrated an equally reliable outcome as water replacing plethysmography.The coefficient of variation (CV) % obtained is on par with water plethysmography, 0.628%.

The coefficient of correlation between (water replacing) plethysmography and volumes calculated using a tape measure is high, 0.932, and the coefficient of regression between the two methods is also high, 0.963 (CI-95: 0.657–1.269, $p < 0.0001$). [71]

The hand and foot can be measured with a tape measure using an elliptical algorithm but is time consuming. It can be used when hand volumes are needed and the water displacement method is contra-indicated, impractical to implement, too time consuming or not available.[75]

The Panel highly recommends limb circumference by a tape measure as a routine assessment of the dimensions of the limb, with simple centimeter measurements at different levels of the limb or for calculation of the volume by applying mathematical formulas concerning geometric solids (cylinder or frustum).

[Strength of recommendation:1 (strong), Quality of evidence:B (moderate) [6-8]*]*

Optoelectronic volumetry:
This methodology determines limb volume by scattering near-infrared rays that use a frame over the subjected limb on a sliding rail. [76]

This method is increasingly used to assess limb volume.

Errors in measuring volumes

The normal extremity volume needs to be measured together with the affected extremity volume every time measurements are made, or else excess volume calculations will be inaccurate if the normal limb decreases or increases in volume. [67]

As with other methods that determine overall limb volume over time, there is a danger in assuming that a smaller limb is better and a larger one worse. But in reality, when the lymphedema does improve, the mobility of the limb will also improve, resulting in an increase of the muscle mass as a consequence of increased activity. Such muscle mass increase leads to a larger limb even though the fluid component contributed by lymphoedema is lower. In contrast, when a heavy arm/leg already has already produced muscle hypertrophy, successful lymphedema treatment (less weight) reduces the load and, thus, the muscle volume decreases. These phenomena should be considered in the assessment of changes in excess calculated limb volume.

There are some strategies that might help to overcome these issues. One example is exemplified by Miller et al (2013), in which they use a weight adjusted volume change formula which is independent of the contralateral limb and which accounts at least for weight changes when the surgical intervention is bilateral. [77]

This is the main reason why some of the techniques such as bioimpedance spectroscopy and tissue di-electric constant measures are increasingly embraced as a more accurate measure of the failure of lymphatic function, *ie,* the presence of excessive fluids in the tissues.

Comparison of the volume measurement techniques

Certainly, each measure we take adds valuable diagnostic information that can help in a more accurate assessment and a better treatment outcome. There are increasing numbers of papers comparing techniques (Jain et al, 20101, Ridner 2007). Results need not be competitive, but should be thought of as complementary. [78-80]

Ultrasonographic Assessment

General Overview

Duplex Ultrasonography (DUS) should include evaluation of the deep, superficial, and local vasculature, and the supra-fascial structures. Venous duplex studies should confirm any associated venous anomalies (valvular incompetence, obstruction, ectasia or aneurysms) and/or exclude venous obstruction as etiology or contributing factor to lymphedema. [1, 2]

The ultrasound evaluation of subcutaneous tissue thickness is a useful parameter to evaluate lymphedema and its response to treatment.
The suprafascial and the subfascial thickness of the edematous tissue are demonstrable through high

resolution echography and tissue compressibility [81, 82]. These are useful measurements that allow periodic assessment of the response to therapy and in monitoring a patient's progress and determining prognosis. [1, 2]

In patients with lymphedema, thickening of the cutaneous, epifascial, and subfascial compartments has been ultrasonographically observed. This contrasts with MRI observations, where the subfascial compartment was shown to be unaffected.[83] High frequency ultrasound (20 MHz) reveals characteristic patterns of cutaneous fluid localization in various types of edema. [1, 2]

In lymphedema, there is a distinctively uniform pattern of distribution. This imaging technique has applications both in differential diagnosis and in therapeutic monitoring, although further refinement may become necessary to better characterize the spectrum of subcutaneous fibrosis that can be encountered in lymphedematous skin. [84, 85]

Ultrasound of soft tissues

The ultrasound study of the patient with lymphedema provides information on the structural tissue characteristics (supra- or sub-fascial distribution of the oedema, presence of ectasias of lymphatic collectors, of lymphatic lakes, connective tissue conditions, thickness of the various skin layers. [86, 87]

The normal appearance of the skin is well-defined on ultrasound, owing to the presence of layers that have a different echo-structure. The demarcation between dermis and subcutis is distinct owing to the different acoustic impedance of the two structurally heterogeneous tissues. The subcutaneous tissue is hypoecogenic due to the presence of adipose lobules interposed in connective shoots and vascular lacunae.

The thickness of the subcutis is quite variable, depending on the corporal seat and body of the patient. The muscular fascia is a hyperecogenic structure separating the subcutis from the muscular tissue running parallel to the skin layer. [88, 89]
With the current axial and lateral resolution capacity, contemporary ultrasound instruments even allow the lymphatic vessels in healthy patients to be seen.

The morphological characteristics of the various skin layers change in lymphedema, in terms of both echogenicity and thickness. There is possibility to use compression of the tissues to study tissue composition [90, 91]

Alterations of the echogenicity

In the dermal layer, the echogenicity is lower in lymphedema than in healthy controls. The reduction of the echogenicity, expression of interstitial oedema, is widespread both in the superficial portion of the dermis (papillary) and in the deep portion (reticular).

This homogeneous distribution differs from the findings of lipodermatosclerosis, in which the reduced echogenicity is mostly located on the superficial dermis and also that of in heart failure, where the edema is mostly in the deep dermal portion. [90, 91]
Instead, the subcutaneous layer in lymphedema has an anechogenic network with polyhedral links that compresses the surrounding hyperecogenic adipose tissue. This network is the expression of the progressive ectasia of the various anatomic levels of the lymphatic system.

Changes in thickness

In lymphedema, all the layers (dermal, subcutaneous and muscular) appear increased in size.
The assessment of the thicknesses is regarded as an essential study procedure for monitoring the development of the lymphoedema and for evaluating the effectiveness of the various treatments.

The thickness of the dermis is measured from the skin surface to the dermis/subcutis interface; the subcutis is on the other hand measured from the dermis/subcutis interface to the muscular fascia. In a more simplified manner, it is possible to measure the subcutaneous tissue thickness from the skin surface to the muscular fascia.

A recent study reported that measuring the resistance of the tissues to compression and thickness of the epifascial tissues using the compression method combined with ultrasound may be of benefit in allowing a more detailed evaluation of the lymphoedema after surgery. [90]

The Panel recommends ultrasound evaluation to at the level of the clinically evident areas of edema in order to define their morphological characteristics and extension, given the cost-effectiveness of this technique on consideration. The thicknesses of the various skin layers (dermis and subcutis) must be measured at pre-defined points.
[Strength of recommendation:1 (strong), Quality of evidence:C (low) [6-8]]

An assessment of the arterial and venous circulation of the limbs is always made with Doppler (probe and appropriate procedures, as described by the relevant guidelines) in order to rule out non-lymphatic pathologies and to check for the presence of co-existing pathological conditions such as recent arteriopathies or venous thromboses and/or post-thrombotic syndrome to depict treatment contraindications. [84]

Radionuclide Lymphoscintigraphy

Radionuclide lymphoscintigraphy (LSG) is a simple methodology, performed with injection of 99mTc-labeled human serum albumin or 99mTc-labeled Sulphur Colloid intra- or subdermally into the first and second web-space of the toes or fingers and the subsequent distribution is recorded with a gamma camera. [92-94]

Movement of the colloid from the injection site, transition time to the knee, groins or axilla, absence or presence of major lymphatic collectors, number and size of vessels and nodes (e.g. popliteal nodes), the presence of collaterals and reflux, and symmetric activity with the opposite side are recorded and used for interpretation.[95-97] Semiquantitative assesment has been reported, and most recently, the technique of quantitative assessment of transit time from the foot to the knee was also validated . [32-34]

LSG is the test of choice to confirm or exclude lymphedema as the cause of chronic limb swelling; it remains the gold standard for lymphatic function evaluation asthe LSG is the only test that can clearly indicate lymphatic function.[1, 2] Radionuclide lymphoscintigraphic findings provide the proper clinical and/or laboratory staging that may be essential for proper clinical management.

LSG, along with clinical evaluation, is the most essential component for the diagnosis of chronic lymphedema. LSG is useful for identifying specific lymphatic abnormalities and has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. LSG can easily be repeated with minimal risk. Data and images obtained from the study identify lymphatic (dys)function, based on visualization of lymphatics, lymph nodes, and dermal back flow (DB) as well as semi-quantitative data on radiotracer (lymph) transport. [1, 2]

However, LSG has not been standardized with regard to the various radiotracers and radioactivity doses, different injection volumes, intracutaneous versus subcutaneous injection site, epi-or

sub-fascial injection, number of injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques.[98]

LSG is a functional study that complements the anatomical information provided by lymphangiography; it offers not only an anatomic study of the subaponeurotic lymphatic vessels, but also a functional assessment. Evaluation can be done in both qualitative and quantitative assays[99] and the quantitative measurements especially can give a functional imaging of the lymphatic transport capacity.

The test reveals various conditions of the tracer clearance including the presence of dermal backflow, and asymmetry-alteration in inguino-axillary nodes (sensitivity- 89%, specificity- 96 %).[100]

In primary lymphedema, there is poor definition of the lymphatic routes with delayed appearance of the regional lymph nodes and possible tracer dermal backflow in the case of hypoplasia, whereas in the case of aplasia there are no lymphatic routes and lymph nodes are not displayed. With quantification a more precise uptake can be measured in the groin. This method needs a normal standard and protocol. The Dutch society of nuclear medicine has provided such a protocol including "normal values of uptake" in groin and "clearance values of the injection side" [101]. Another method of investigating the lymph transport can be performed by the use of a transport index, where an index below 10 is normal. The index combines visual assessment of five criteria: temporal and spatial distribution of the radionuclide, appearance time of lymph nodes, and graded visualization of lymph nodes and vessels. [102]

In secondary lymphoedema, transport is decreased or absent combined with various grades of dermal back-flow. Sometimes collateral circulation, lymphocele, and lymphangioectasies can also be seen. Here quantification is also useful, especially in comparisons with the contralateral limb to see if there is already a pre-existent lymphatic impairment. This is often the case in so-called post infectious secondary lymphedema, which shows to be a primary impairment. [103-105]

Recently lymphoscintigraphy and CT scan can be combined to improve diagnostic accuracy by retrieving functional (scintigraphy) and anatomical (CT) data together [106-108]

The Panel recommends lymphoscintigraphy for the evaluation of the lymphatic system from a morpho-functional point of view as pre-treatment assessment. It is also recommended as a follow up assessment of therapy as well as natural disease progression for comparison with basic values at start.
[Strength of recommendation:1 (strong), Quality of evidence:A (high) [6-8]]

Although the absolute majority of the Panel gave the recommendation to 1 (strong) and A (high) to LSG as a non-invasive test for basic evaluation of the lymphedema, the current quality of LSG remains controversial because of poor image resolution. LSG is unable to detect edema in the lymphedematous limb and infrequently mis-identifies dermal backflow. Besides, it is also known for false positive findings (e.g. erisypelas) in up to 10% of studies. However, LSG maintains its leading role as a functional test in the initial diagnoses of an enlarged limb although it hardly displays the anatomical abnormalies of lymph vessel and lymph node (cf. oil contrast lymphgraphy).

Fluorescent lymphography with indocyanine-green (ICG)

General overview

Near-infrared fluorescent technique using indocyanine-green (ICG) was developed to visualize lymph channels and nodes. Its first documented advantage was in sentinel lymph node labeling allowing a precise identification. It is also able to display the superficial lymphatic map of the examined body part and to detect abnormalities such as dermal backflow.[109, 110]

Using minor modifications the method is able to demonstrate the propulsion of lymphatics and the effects of distinct physiotherapy to enhance lymph flow. It is of importance in the assessment of the efficacy of surgical interventions. [111-114]

This relatively new ICG lymphography[115-118] is now accepted as a comparatively easy and non-invasive means of assessing superficial lymphatic function. It can provide valuable information of lymphatic flow for use in lymphatic surgeries such as lymphovenous shunts and vascularized lymph node transfer. It is also effective as a diagnostic tool in the general assessment of lymphatic function.

The non-invasive and non-radioactive nature presents a viable alternative to traditional lymphoscintigraphy, at least for superficial lymphatic functional assessment. [1, 2]Side effects are rare but may be severe if an allergy is present. There are few cross allergies with fluorescein angiography but ICG contains iodine and people with an allergy to iodine (shell fish, for example) are at risk for serious reactions. [119-121]

Qualitative assessment of abnormal lymph circulation

Lymph flow obstruction leads to lymph back flow that is visualized as dermal backflow in various patterns on ICG lymphography. ICG lymphography pattern changes from normal linear pattern to abnormal dermal backflow patterns in obstructive lymphedema as the lymphedema progresses. [115-118, 122]

The staging system based on ICG lymphography dermal backflow findings, are useful for early diagnosis of lymphedema, because the dermal backflowstages can be subdivided into asymptomatic lymphedema (ISL stage 0) stage I (splash pattern) and stage II (stardust pattern).[139] This differentiation is clinically important, since the splash pattern is a reversible change, but the stardust pattern has been shown to be an irreversible change.[151,152]

Quantitative assessment of lymph contractility

ICG lymphography can visualize lymph flow in real time, thus allowing assessment of lymph pump function , such as transit time, lymphatic pressure, and ICG velocity.[115-118, 121, 122]
ICG velocity decreases with progression of lymphedema and this can be used to assess the efficacy of therapeutic interventions.

Prediction of the condition of the lymphatic vessels'

Prediction of the lymphatic vessels condition is important for the preoperative assessment of lymphatic surgeries. In regions with diffuse patterns, lymphatic vessels are likely to be too sclerotic to create bypasses, and the treatment efficacy of lymphovenous shunts would be minimal. [123, 124]

Tonometry

The tonometer is an instrument developed by Piller and Clodius in 1976 that is used to determine the tonicity of the dermal and subcutaneous tissue by measuring the compressibility of the tissues.

Tonicity is defined as the degree of tissue resistance to mechanical compression, and is therefore an objective measurement of the subjective parameter of the compressibility of the edema. Basically, the tonometer measures the degree and change of the compressibility of the tissues over time quite accurately subject to the action of a standardized weight. [125]

Some authors have conjectured they are able to get information about the biochemical characteristics of the edematous tissue by studying the absolute value of the compressibility and deformability of this tissue. Certainly, even if tonometry still does not have sufficient studies, it seems to be a good methodology for quantitatively and objectively evaluating characteristics of the edema , which have been assessed up until now only semi-quantitatively and subjectively, like the pitting indentation and consistency of the tissue.[126]

This method does not give reliable and reproductive figures in other comparative patient groups. Therefore, for clinical use, other methods are of better discrimination. [127])
However, with recent changes to the instruments electronics it is likely that these problems can be overcome. [128, 129]
In the interim period, however it can be used for research purposes.

Bioempedance Spectroscopy (BIS)

Bioimpedance is a noninvasive method mostly used for estimating body composition based on the electrical conductive properties of various tissues. [130]
Commonly known as BIA (bioelectrical impedance analysis), it involves the use of low frequency (typically 50 KHz) electrical currents travelling through the extracellular fluid and tissues.
This technique is able to identify, even in a segmental setup, and qualify the fluids in the limbs. The test is highly sensitive and specific [131], but it can suffer low reproducibility if the test is not correctly standardized .

Fu et al (2013), however, have recently investigated the benefits of the use of the BIA ratios (indicated as the L-Dex Ratio) and found not only was it highly reliable among healthy women, survivors at risk of lymphoedema and for those with lymphoedema, although the interclass correlation and confidence interval was less and wider in the later group. [132]

Notwithstanding this an L-Dex ratio with a cut off of more than 7.1 could discriminate between those at risk to develop lymphedema and those with lymphoedema with 80% sensitivity and 90% specificity. Further BIA ratios were found to be well correlated with limb volumes determined by circumference measurements. While the L-Dex ratio cut off at 7.1 means some 20% of true lymphedema cases are missed. The L-Dex Ratio therefore does not seem an optimal clinical tool . [132]

It seems that with long lasting lymphedema or lymphedema stage 2-3 (more adipose tissue formation and fibrosis) the percent false negative values of BIA will increase.[131] Therefore, it may not be suitable for treatment evaluation or follow-up of lymphedema in these stages until research brings further data.

Tissue Dielectric Constants (TDC)

Measurement of TDC is a method to measure the local content of water in skin and subcutaneous tissue in a quantified way using an electromagnetic wave of 300 MHz. The portion of the wave reflected depends on the dielectric constant of the tissue, which itself depends on amount of water (intra- and extracellular) in the tissue. Water absorbs the electromagnetic wave, i.e. when TDC is calculated high water content gives a high TDC. TDC has previously been used to measure

lymphedema patients treated with CDT including manual lymphatic drainage.

This relatively recent technique is also gaining momentum in terms of its use. (Mayrovitz, 2007; Mayrovitz, et al 2010;) Unlike BIA which can measure segmental or whole limb fluids, the TDC can measure site specific fluids at specified depths.

Generally most studies report the best measuring depth to be 2.5 mm. Basically the operation of the units rely on the sending and receive of a 300 Mhz signal by the head rested gently on the skin, the percent of the electro- magnetic wave which is reflected back is dependent on the amount of free and bound water in the tissues. [133-135]

Comparisons between basic tissue compositional measurement techniques

Comparisons between perometry and tape measurement techniques have been described earlier in this chapter, but there are also an increasing number of comparisons between other tissue measurement techniques.

For instance, Jain et al. (2010) compared BIA with perometry and found that bipimpedance spectroscopy is a reliable means of assessing upper limb lymphedema. Ridner et al. (2007) compared tape measure volumes with volumes assessed with perometry and with BIA measurements and linked them to self-reported arm symptoms and found that all measurement methods correlated with self reported arm swelling but only arm circumferences and BIA measurements correlated with arm firmness. [78, 79]

Although each one has its own unique merit to improve diagnostic accuracy, it has a limited value as an independent measure of the lymphedema for early detection.
claim the best measures of lymphedema as independent

Computerized Tomography (CT)

CT examination is able to evaluate the skin, subcutaneous and muscular compartment, identifying the density, thickness and morphological characteristics (presence of thickened or fibrotic interlobular septa. [30, 31, 136] This examination is not devoid of side effects and contraindications aside from the radiation hazard especially amongst the pediatric group. It is recommended for complicated patients, for research purposes or for accurate volume measurement. It is also desirable when other pathology is suspected (e.g. cancer recurrence). [137, 138-140]

However, the newly introduced Multislice CT (MSCT) with 64 detectors is capable of delivering 3D modelling of the limb and reconstruction by volume rendering technique (VRT) [141] in a special "low dose protocol" requiring a negligible dose of radiations of about 0,5 μSV by leg and does not require contrast injection.

The limb volume computation is accurate with this 3D reconstruction of the limb by VRT to characterize excess fluid limited to the skin and subcutaneous tissues.
This 3D modelling providing several information: total amount of fluid of the limb (global quantification), the amount of fat tissue, topography of the extra fluid along the limb (proximal, distal, segmental, dorsal, ventral), and the precise location of the extra fluid inside each tissue: skin, subcutaneous, interstitial tissue, and muscle.

Lymphedema can also be characterized by some common CT findings for diagnostic purposes,

mainly by the thickening of the subcutaneous compartment but also increased fat density, thickened perimuscular aponeurosis, and a typical honeycomb pattern in most patients.

Evaluation of such fibrosis also provides information about the length of evolution of the lymhpedema. Severity grading of lymphedema based on this could be used to classify the patients. In addition, the therapeutic response to compression therapy can be monitored efficiently.[142, 143]

Differential diagnosis with MSCT is also possible by the ability to differentiate fat tissue from fluid, to identify subfascial (muscular) edema and look for of a local cause together with MRI.

A study performed by Smith et al.[144]showed that MSCT is comparable to water displacement (the only validated method) in both precision and accuracy of limb volume measurement. Accuracy of MSCT assessment[142] for diagnosis has been reported for lymphedema with 93% sensibility and 100%-specificity.

In summary, the use of MSCT to measure the limb volume and to assess lympedema is accurate, validated and reproducible. Despite the administration of a low dose of X rays, it appears to be superior to the water displacement method (which is today the only validated technique), because it also has the advantage of measuring the different segments of the lower limb (foot, ankle, leg, thigh) separately and to specify the exact location of the edema inside the tissues (skin, sub-cutaneous, fat, muscle).

It is a tool for diagnosis and also helpful to provide information about the etiology of the lymphedema and its severity grading. This technique, as well as MRI, is particularly recommended for research purposes and trials.[143]

MR Imaging (MRI)

MRI with or without contrast is indicated for further detailed evaluation of tissue overgrowth, pelvic pathology obstructing lymph drainage or malformations among the patients with a combined form of vascular malformations (e.g. Klippel-Trenaunay Syndrome).[146, 147]

In lymphedema, the MRI images reveal a characteristic distribution of edema within the epifascial compartment, disclosing a honeycomb pattern along with thickening of the skin. In contrast, in venous edema, both the epi- and subfascial compartments are affected, while in lipedema, there is fat accumulation without fluid.[148, 149]

MRI is also helpful in the identification of lymph nodes, enlarged lymphatic trunks, and in the differentiation of the various causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI may complement the functional assessment provided by lymphoscintigraphy. At times, these complementary sources of information are necessary to establish the diagnosis and to make the requisite therapeutic decisions. [1, 2, 38]

Non-contrast heavy T2 weighted MR imaging is therefore, an essential tool to display dilated superficial lymphatic collector and deep lymphatic trunks in the inguinal, iliac and lumbar branches. T2 weighted MR imaging is capable of localizing stagnant water in the tissue and highlighting the position and severity of tissue edema. With a fat saturation sequence MRI, it was possible to identify other pathological changes in the soft tissue, such as fat deposits and fibrotic tissue. MRI could be used for accurate limb volumetry however financial burdens limit this application only to research purposes.[150]

MR Lymphangiography (MRL)

General Overview

MR lymphangiography using the paramagnetic contrast agent gadobenate dimeglumine (Gd-BOPTA) is a relatively new imaging approach to assess lymphatic system architecture and lymph drainage in extremities affected by lymphedema . [151-152]It is able to provide comprehensive information about the precise anatomic and functional status of the lymphatic system.

High resolution Lymphatic imaging

The contrast enhancement of the lymphatic system was seen soon after injection. The contrast agent generated clear images of lymphatic vessels and lymph nodes with a low background. On post-contrast MR, consistently enhanced images of the lymphatic channel were visualized in the lymphedematous limbs. The signal intensity increased and the channels gradually become totally opacified with time. The number of contrast enhanced lymphatic vessels in primary lymphedematous limbs varied from a single vessel to numerous vessels. [151] Both superficial and deep lymphatic vessels may be visualized in some cases. It is able to make the classification of lymphatic system malformations in primary lymphedema[153] and lymphedema related syndrome[154] with use of MRL. The lymphatic collectors in secondary lymphedema extremity are tortuous and significantly dilated. Other obvious damage of collecting lymphatic vessels in obstructive lymphedema included vessel disruption, lymph leakage or regeneration of small lymphatic between the broken vessels on MR lymphangiogram . [155]

Dynamic and real time observation of contrast enhanced lymph transportation in lymphatic channels

Enhanced lymphatic vessels around the ankle are clearly visualized soon after the injection using post-contrast MRI. The flow of contrast material within the vessels can be detected on a series of dynamic images, and the length of opacified lymphatic vessels is measured on a selected vessel. The speed of contrast transportation is calculated and expressed as cm/min . [151]

High resolution lymph node imaging

The abnormalities of inguinal nodes in primary lymphedema limbs observed o MRL imaging are: no visualized node; small nodules, fibrotic node with homogeneous higher density, node with irregular border and hemogeneous architecture and partial enhancement, enlarged nodes with increased number. [151] In secondary lymphedema after pelvic malignant treatment the morphological changes of inguinal lymph nodes are reduced in number, smaller in volume, partial or no contrast enhancement. Contrast enhanced MRLis also a sensitive modality in the diagnosis of malignant peripheral lymphedema and the identification of inguinal lymph node metastasis in patients with various tumor origins. [156]

Lymph nodes transportation function

The post-contrast MR images of lymph nodes show remarkable asymmetrical accumulation of contrast agent between the nodes of edematous limbs and contralateral limbs in patients with unilateral lymphedema. The post-contrast enhancement of node/muscle SI ratio in lymphedematous limbs is significantly lower than in contralateral limbs. The nodes of edematous limbs display a decreased slop and slower wash-out, remarkable reduced peak enhancement, and significantly longer time to peak enhancement. [151]

Comparison of MR lymphangiography and lymphoscintigraphy

The quality of MRL imaging in mapping lymphatic patterns is comparable to that of direct lymphangiography with use of an iodine oil contrast agent, and is able to classify lymphatic anatomic abnormalities. The detection rate of lymphatic vessels and lymph nodes with MRL is much higher than that found with lymphoscintigraphy. Compared with lymphoscintigraphy, MRL is more sensitive

and accurate in the detection of anatomical and functional abnormalities in the lymphatic system in extremity lymphedema. [157]

The Panel recommends MRI and MRL examinations when lymphedema (including malignant lymphedema) is suspected and when studying the lymphatic vessels and lymph nodes in preparation for micro-surgical operations, as well as for studying the etiology of the disease. [Strength of recommendation:1 (strong), Quality of evidence:A (low) [6-8]]

Non-contrast Radiography

X-rays of bones will identify limb length discrepancies, bone abnormalities, or phleboliths in patients with combined lymphatic malformation and venous malformations. Bone scanogram is specifically designed for the assessment of bone length (e.g. angioosteodystrophy).

Dual Energy Xray Absorptionmetry (DXA)

DXA could also be used to estimate the excess fat, muscle, and bone tissue in lymphedematous limbs. [52, 53, 158]

Invasive Tests

Oil Contrast standard lymphangiography/lymphography

Kinmonth introduced the standard lymphangiography (LAG) to clinical practice in 1952. (18). A lipid-soluble ultrafluid contrast medium (Lipiodol Ultrafluid) is injected into the lymphatic vessel after isolation and cannulation of the lymphatics of the dorsum of the foot with microsurgical technique so that the lymphatic network and the lymph nodes can be seen.

LAG provides data regarding the number, caliber, course of the lymphatic vessels, and the lymphatic-venous connections, thus giving a morphological evaluation of the lymphatics. However, the technique is burdened by many complications: pain, lymphangitis, dermatitis, thrombophlebitis, fever, headache, vomiting, diarrhea, up to more grave situations such as pulmonary, cerebral, renal, hepatic embolism or anaphylactic shock. Lymphangioghraphy is therefore, no longer recommended for general routine use and it may be added as a road map only when studying the lymphatic circulation in preparation for a lymphatic micro-surgical operation.

However, when this conventional oil contrast lymphangiography[56-58] is coupled with CT scan, it allows a more accurate assessment of disease extension, as well as the site of the obstacle and source of chylous leakage. LAG is still advantageously employed in selected patients with chylous dysplasia and gravitational reflux disorders in order to define more clearly the extension of the pathologic alterations and sites of lymphatic and chylous leakage. These are the only diagnostic investigations that can clearly demonstrate pathologies of chylous vessels, chylous cyst and thoracic duct in cases of chylothorax, chylous ascites, protein losing enteropathy .[159, 160]

The main indications for the use of direct oil contrast lymphangiography are represented by the pre-operative assessment of patients affected by lymphatic and chylostatic disorders: chyloperitoneum, chylothorax, , chyluria, chylo-colpometrorrhea, chylo-lymphorrhea, and chylous joint effusion.

Under local anesthesia the blue dye is injected in the first interdigital space of both feet in order to delineate the transit site of the main lymphatic collectors and perform a microincision to ensuring the location of a proper lymphatic vessel for the cannulation.

The isolation of the lymphatic collector from the surrounding tissues mandates the use of a microscope (25-30x) to accurately "prepare" the lymphatic collector with an atraumatic technique, and avoid damages to the lymphatic wall and to the surrounding lymphatics .

During the injection, fluoroscopy controls are necessary to highlight possible lymphatic-venous fistulas, with a typical radiological imagine of "caviar eggs"; to avoid the risk of pulmonary microembolism, the manual injection is safer to be able to stop the examination, if needed.

Once the contrast is injected entirely, the patient undergoes a CT examination, which shows the presence of the contrast medium in the cisterna chyli and the thoracic duct as well as the disease extension(e.g. the obstruction site ; chylous leakage source). 3D-CT scan shows the relationship between lymphatic-lymphnodal structures, providing precise location of chylous dysplasia and/or fistulas. [161-163]

Quantative and qualitative lymphangiography/lymphography cannot be recommended as a routine evaluation, due to the above mentioned risks but may be included only when studying the lymphatic circulation in preparation for a lymphatic micro-surgical operation. (21)

Indirect lymphangiography

An indirect lymphangiography can be made by injecting a water-soluble lymphotropic contrast medium intradermally. Owing to the contrast characteristics, only lymphatic collectors close to the injection area are seen . Given that it is preferable to also see the lymph nodes, it is not recommended for routine clinical use.

Molecular diagnostic flow chart for patients with primary lymphedema as major clinical sign

Investigation of genes involved in primary lymphedema may be useful to complete the clinical picture of patients. Moreover, when the test is positive, it may be possible to determine whether other family members carry the same pathogenic mutation. The results of genetic tests for molecular study of genes involved in primary lymphedema may enable better clinical management of patients and relatives, if any, as well as savings in public health costs.

For example, it may be possible to determine women at risk for secondary lymphedema among the population of breast cancer patients undergoing medical treatment and/or surgery (Finegold et al. 2012). [164] In case of lymphoedema associated to leukemia (Emberger Syndrome) the genetic study of mutation of GATA2 gene (Ostegard et al. 1011) [165] is also indicated. David N. Finegold, Catherine J. Baty, Kelly Z. Knickelbein, et al. Connexin 47 mutations increase risk for secondary lymphoedema following breast cancer treatment. Clin Cancer Res 2012;18:2382-2390.

However, the majority of genetic mutation are demonstrated in sporadic (non familial or Mendelian) case of lymphoedema. In this case the genetic transmission to the 'offspring' is not demonstrated. In familial lymphoedema the study of subclinical subjects with positive genetic mutation is indicated by means the lymphoscintigraphy (variable expressivity). [166, 167]

In the last 20 years, intense research into the lymphatic system has shed light on the pathogenesis of

lymphatic-related disorders such as lymphedema. Although the phenotype of lymphedema reflects a great heterogeneity of associated clinical signs, widely varying age of onset and variable clinical expression, molecular biology is useful for characterizing gene defects in a fraction of affected individuals)[166, 168,

Albeit with different incidences, mutations in the genes FLT4 and FOXC2, and in genes VEGFC, GJC2, HGF and MET, have been correlated with manifestation of phenotypes in which primary lymphedema is the major clinical sign. [166, 169-173]

Current data suggest that the first-level genetic test on the genes FLT4 (analysis limited to the coding region for TK domains) and FOXC2 explains the molecular defect in about 25% (12/46) of Italian patients, irrespective of the presence of distichiasis (Michelini et al. 2012). [174]

Another recent data (Ferrell et al. 2008; Ferrel et al. 2010; Ostergaard et al. 2011; Gordon et al. 2013) suggest that in patients without alterations in FLT4 and FOXC2, it is reasonable to seek the genetic defect using a new second-level test, involving direct sequencing of the coding region of the genes VEGFC, HGF, MET and GJC2. [165, 173, 175, 176]

To increase the efficiency, in terms of costs and time, a next-generation approach may be adopted. In case of negative results in the second-level of analysis, a non diagnostic experimental strategy, based on whole exome sequencing of patients and selected family members, can be used to find the molecular defect. [177]

In second step, these genes can be evaluated to determine whether they cause the phenotype in other patients (sporadic cases and probands from families with few affected members) by direct sequencing. [177]

Clinical and Laboratory Staging

There have been substantial efforts over several decades to provide proper clinical staging of lymphedema in conjunction with a proper classification. There are many different staging systems[15-17], including a three staging system (Stage 1 through 3) proposed by the International Society of Lymphology ; more recently, Stage 0 has been added to this schema. [1, 2]

Most of the currently available staging systems reflect only tissue turgor and limb shape, etc and neglect other critical clinical information (e.g. number of major joints with changes in tissue composition) as well as socioeconomic status, or physical limitations, to reflect quality-of-life (QoL) considerations properly.[19-21]

Therefore, many new proposals were made to compensate for such discrepancies; these include the Lymph CEAP classification by Europeans and U.S.-based combined staging of two separate Clinical and Laboratory staging based on the lymphoscintigraphic findings.- [15-17, 178, 179] None of the current staging systems are able to meet the mandate as contemporary guidelines for improved management of lymphedema in different stages. [1, 2]

Lipedema - Differential Diagnosis

Lipedema is the most common disorder to be confused with lymphedema; it is an infrequently recognized clinical entity affecting nearly exclusively women.
The diagnosis of lipedema is relatively simple using patient history and clinical examination. [180-184]

There are striking features to facilitate the recognition of this disproportional obesity. In the early stages of the disorder, the only clues may be the bilateral fat-pads right below the inner sides of the knees and the disappearance of the concave spaces on both sides of the Achilles tendon (ie, the filling of the retromalleolar sulcus). [181-183]

With progression, the characteristic 'stove pipe' legs appear; however, the feet remain spared and the fat deposits begin abruptly above the ankles (cuffing sign, sparing of feet) *[4,5]. In case of arm involvement fat deposition abruptly ends at wrists leaving hands unaffected. *[4,5] In contrast to lymphedema, Stemmer's sign is always negative in pure lipedema and the edema is hardly or non-pitting.[181-184] Two further leading hallmarks are the 'easy bruising' and aching dysesthesia. [181-184]

Lipedema, especially in advanced stages, quite frequently co-exists with impaired lymphatic or venous function that may strongly modify the original limb shape resembling the features of identical vascular abnormality. [182-185]

Combined forms with lymphatic, venous insufficiency, or morbid obesity can be difficult to accurately diagnose, therefore various non- or minimally invasive tests might efficiently assist clinical assessment.

High resolution ultrasonography can distinguish lipedema from phleb- or lymphedema with high sensitivity.[186] According to Monnin-Delhom *et al*., computed tomography scan has a sensitivity of 95% and specificity of 100% for the diagnosis of lipedema. [142]

Altered microcirculation with increased permeability results a large amount of interstitial fluid thus increased lymph flow is visualized by lymphscintigraphy in early stages of lipedema. If lipedema remains untreated the increasing amount of interstitial fluid warrants a higher transport capacity of lymphatic conductors. This transitional intensive function exhausts the lymphatic vessels modifying the phenotype from lipedema to lipo-lymphedema as a result of lymphatic insufficiency.[187]

Fluorescent microlymphography also displays lymphatic microaneurysms and dilated vessels of the uppermost lymphatic network, indicating that lymph vessels might also be involved in the pathogenesis. [188]

Epilogue

Enormous advance in the diagnostic technology through last two decades confirmed the venous and lymphatic systems as mutually dependent 'dual outflow' system of the circulation. Although these two systems function in entirely different rheodynamic conditions with different characteristics, they are one 'inseparable' system complementing each other as 'mutually interdependent' system.

We attempted to break current concept of Phlebology and Lymphology artificially separating the venous and lymphatic system with a new concept to incorporate the veno-lymphatic system as one. After all, the insufficiency or overload to one of these two systems allows the other to play an additional role to compensate for the fluid return. Simultaneous evaluation of these two systems are therefore, mandated for any one of two system ailments (e.g. evaluation for the chronic lymphedema for chronic venous ulcer).

It is our hope that this document will stimulate further inquiry and discussion regarding all aspects of lymphedema diagnosis within this boundary of new concept and that it will form a starting point for future discussions and, ultimately, that it become a "living document," amenable to periodic updates

and revisions that will incorporate new ideas, technologies, and directions.

BB Lee and Pier Luigi Antignani

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Appendix A. Ratings of the quality of evidence and grading recommendation system used in the Consensus

Table 1. Grading Recommendations According to Evidence[1] (Chest, 2006;129:174-181.)

Grade of Recommendation/Description
1A/strong recommendation, high-quality evidence
1B/strong recommendation, moderate quality evidence
1C/strong recommendation, low-quality or very low-quality evidence
2A/weak recommendation, high-quality evidence

2B/weak recommendation moderate-quality evidence
2C/weak recommendation low-quality or very low-quality evidence