Chronic edema of the lower extremities: international consensus recommendations for compression therapy clinical research trials

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Chronic edema is a multifactorial condition affecting patients with various diseases. Although the pathophysiology of edema varies, compression therapy is a basic tenant of treatment, vital to reducing swelling. Clinical trials are disparate or lacking regarding specific protocols and application recommendations for compression materials and methodology to enable optimal efficacy. Compression therapy is a basic treatment modality for chronic leg edema; however, the evidence base for the optimal application, duration and intensity of compression therapy is lacking. The aim of this document was to present the proceedings of a day-long international expert consensus group meeting that examined the current state of the science for the use of compression therapy in chronic edema. An expert consensus group met in Brighton, UK, in March 2010 to examine the current state of the science for compression therapy in chronic edema of the lower extremities. Panel discussions and open space discussions examined the current literature, clinical practice patterns, common materials and emerging technologies for the management of chronic edema. This document outlines a proposed clinical research agenda focusing on compression therapy in chronic edema. Future trials comparing different compression devices, materials, pressures and parameters for application are needed to enhance the evidence base for optimal chronic oedema management. Important outcomes measures and methods of pressure and oedema quantification are outlined. Future trials are encouraged to optimize compression therapy in chronic edema of the lower extremities.

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An international panel of experts convened a day-long conference in Brighton, United Kingdom, in March 2010, to examine the current state of clinical practice and evidence base to support the use of compression modalities in managing chronic edema. This expert panel organized by the International Compression Club (www.icc-compressionclub.com) is a recognized entity in providing evidence-based consensus documents, most recently regarding compression therapy for breast cancer related lymphedema.[1] The goal of this session was to examine gaps in the current literature, investigate disparities in current clinical practice and make recommendations for future clinical trials that may further optimize practice in compression management of patients with chronic edema.

The aim of this document was to present prerequisites for future clinical trials in an effort to close the identified gaps and answer important clinical questions. A secondary purpose of this document was to inform industry of trials needed to examine the effectiveness of materials commonly used to treat chronic edema.

For the purposes of this consensus document, consideration was given only to lower extremity chronic edema; defined as persistent edema, duration of greater than three months.[2]

Scope of the clinical problem

Chronic edema of the lower extremity is a frequently occurring condition. Prevalence rates are reported between 7% and 20% based on gender.[3] Chronic edema is more prominent with advanced age [2, 3] and is commonly documented in association with conditions such as renal failure, heart failure venous insufficiency and prolonged immobility.[4-7] However, due to disparity in education vast deficits exist in the knowledge base of health care providers who often manage these conditions.

Pathophysiology differential diagnosis

Chronic edema may be the clinical manifestation of multiple and varied medical conditions such as; immobility, sedentary lifestyle, obesity and other underlying medical conditions of the heart, lungs, kidneys or liver and is ultimately characterized by an imbalance between extravasation of fluid from the blood capillaries into the tissue and its reabsorption by lymphatic drainage.[8] Swelling in the lower extremities is especially troubling as the body system must work against gravity which further complicates fluid return. Common pathophysiology of chronic oedema and their causative factors are summarized in Table I.

Regardless of the pathogenesis, swelling results when fluid filtration from blood capillaries and venules exceeds the lymphatic system's ability to remove extravasated fluid. In peripheral tissues such as the dermis, subcutis and muscle, venous reabsorption of fluid is only transient when Starling forces change. Otherwise in the steady normal state, tissue fluid is reabsorbed via the lymphatic system.[9] Therefore, any chronic edema indicates lymphatic failure.

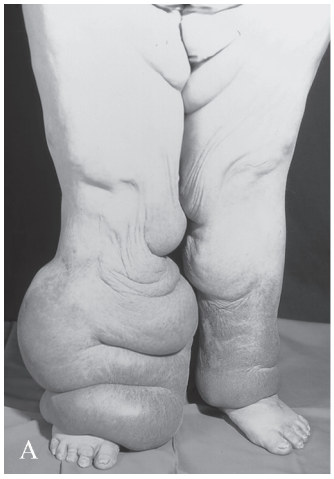
Interstitial protein concentration and therefore interstitial colloid osmotic pressure is finely regulated. The bulk, rather than the concentration of tissue proteins, increases with the chronicity of edema and incites changes in the tissues associated with inflammation and deposition of dermal collagen and fat.[10, 11] Such tissue changes impact lymphatic vessel function and undermine the efficiency of protein and water absorption into the initial lymphatics.[12] Chronic changes result in reduced contractility and pumping capability of larger lymphatics contributing to further fluid congestion.

Edema of any pathophysiological origin, when chronic, will result in this state of lymphatic failure.[13] At this common endpoint compression therapy is recommended based on the presentation of the limb and tissue changes rather than on the causes of swelling.

Swelling manifestations may be alleviated with elevation, using gravity to assist fluid return to the proximal trunk.[14] Elevation reduces venous pressure and therefore filtration rate and lymph load contributing to improved fluid absorption during periods of low capillary filtration such as with elevation. Acute swelling may be aided initially by pharmacological interventions to induce diuresis especially in swelling conditions related to cardiac or kidney dysfunction.[15, 16] Long-term administration of diuretics may, however, create an imbalance of the rennin-angiotensin mechanism and actually worsen chronic edemas not due to cardiac or nephrological origin. Therefore, their use is limited in managing chronic

TABLE I.—*Common causes of chronic lower extremity edema.*

Pathophysiology	Clinical conditions
Increase of venular pressure	Venous reflux or obstruction Cardiac Insufficiency Immobility – muscle pump failure Lower extremity dependency
Increased capillary permeability	Hormones Drug side effects Vasodilation (heat) Inflammation Diabetes Hypertension Exercise
Reverse osmotic pressure difference	Renal failure Malnutrition Blood plasma protein deficiency
Lymphatic failure	Functional decompensation Primary lymphatic deficiency
Lipoedema	Unknown



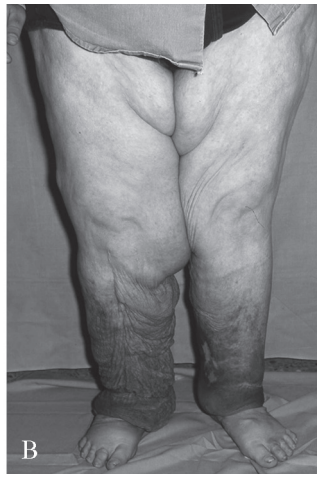


Figure 1.—Limb volume decongestion after 20 treatment sessions over 4 weeks using multi-layer compression bandages (courtsey of Isabel Cordero).

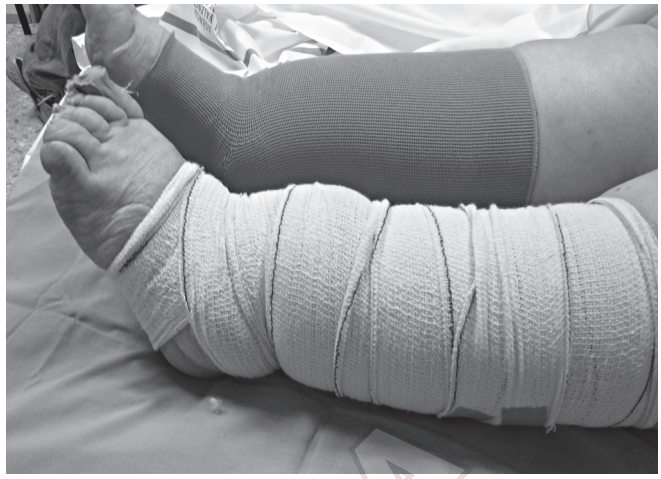


Figure 2.—Poorly applied compression bandage materials (left leg) and poorly fitted compression hosiery (right leg) (courtsey of Isabel Cordero).

edema.[16] In cases where acute infection causes significant inflammation, swelling may result. In these instances antibiotic use will resolve the infection and aid in reduction of swelling. Acute edema is transient and will resolve when the underlying pathological mechanism is alleviated.

Compression reduces capillary fluid filtration from blood to tissue by changing Starling Forces. Compression combined with exercise or movement enhances lymph drainage (both interstial protein and fluid absorption from tissue to initial lymphatic and transport within initial lymphatics). [17]

The differentiation between acute and chronic edema is often not recognized in medical domains and therefore chronic edema is often incorrectly and poorly diagnosed and managed. When edema becomes chronic the associated circulatory, lymphatic and soft tissue changes require more astute and comprehensive management with compression therapy as a primary component of treatment.[18]

Clinical challenges

Chronic edema is managed in a variety of clinical domains, typically based on the etiology of the swelling. The disparate nature of this approach lends itself to inadequate medical management. Medical providers frequently do not recognize the need for specific interventions to manage chronic edema and aside from pharmacological interventions compression therapy is generally overlooked due to poor provider knowledgebase.[19] Compression therapy is proven to be a very effective treatment modality (Figure 1) but requires the application of the correct modality based on the presenting signs and symptoms of edema and the associated tissue changes.[14] Incorrect prescription and application of compression therapies can further complicate edema causing pain and discomfort resulting in non-compliance with therapy [19] (Figure 2). Few medical providers are knowledgeable in the appropriate application of correct compression therapy modalities as the clinical knowledge and skills are relatively specialized.[20, 21]

Ongoing assessment of treatment effectiveness is necessary and best achieved through continued interval medical follow up often throughout the patient's lifetime to maintain decongestion and prevent further fluid refill.[22] Even when compression modalities are well-fit and correctly prescribed, proper counseling from the medical provider provide appropriate education and guidance otherwise, patient compliance may suffer.[23, 24] Follow-up is also necessary for continued reassessment of the therapeutic benefits of the intervention.[14]

Shortcomings in the current literature

Evidence-based advice for the appropriate intensity, duration and mode of compression is ill-

TABLE II.—*Evidence for compression efficacy in edema reduction of the lower extremities.*

Study aim	Methodology	Comparison	Outcome	Reference
Prevention of leg swelling during long haul flights	Systematic review	10 RCTs (N.=2856) 10-20 mmHg stockings vs. no compression	Edema prevented by stockings	Clarke M *et al.* 2006 [41]
Occupational leg symptoms	Systematic review	Stockings (10-20 mmHg) vs. placebo or no treatment vs. stockings (>20 mmHg)	Compression with 10-15 mmHg is effective in preventing edema and complaints. Less pressure is ineffective and higher pressure may be of no additional benefit	Amsler F *et al.* 2008 [42]
Symptomatic leg edema in venous patients (CEAP C1-C3s)	RCT	Stockings (10-15 mmHg) vs. placebo-stockings	Significant reduction of swelling and improvement of QOL	Vayssairat *et al.* 2000 [39]
Venous edema in pts with chronic venous disease	RCT	30-40 mmHg stockings vs., horse chestnut extract	Reduction of leg volume (12 weeks) in both groups	Diehm C *et al.* 1996 [38]
Venous edema CEAP C(3)-C(5	Two phase II clinical studies	Sustained (SPC) vs. intermittent pneumatic compression (IPC)	Higher pressure associated with greater volume reduction in subjects with chronic venous edema.	Vanscheidt W *et al.* 2009 [43]
Venous edema in acute DVT	RCT	Inelastic bandages vs. stockings (20-30 mmHg) vs. bed-rest	Volume reduction with bandages and stockings, not with bed-rest	Blättler W *et al.* 2003 [45]
Prevention of post-thrombotic syndrome after proximal DVT	RCT	Compression stockings (ready-made) 20-30 mmHg vs. no stockings	Reduction of PTS after >2 years	Prandoni P *et al.* 2004 [47]
Prevention of post-thrombotic syndrome after proximal DVT	RCT	Bandages vs. stockings (20-30 mmHg) vs. initial bed-rest 2 y after acute DVT	Bandages and stockings less edema than bed-rest (Villalta scale)	Partsch H *et al.* 2004 [50]
Prevention of post-thrombotic syndrome	Systematic Review	Review: 3 RCT Stockings 30-40 mmHg vs. no intervention	Stockings prevent PTS	Kolbach DN *et al.* 2004 [48]
Therapy of PTS	Systematic Review	Review: 2 RCTs including IPC 15 vs. 50 mmHg	Higher pressure better than lower pressure	Kolbach DN *et al.* 2003 [49]
Lower limb lymphedema	RCT	Inelastic bandages vs. stockings	Bandages better than stockings for the initial therapy of lymphedema	Badger C *et al.* 2000 [53]
Lower limb lymphedema	experimental, controlled comparative study	Reduction of leg volume and bandage pressure under short-stretch bandages	Volume reduction is the most important cause for the loss of bandage pressure. at 2 hours and 24 hours after application of a new bandage	Damstra R *et al.* 2008 [54]
Lower limb lymphedema	Cohort study	Elastic stockings during 5 years	Compression stockings are associated with long-term maintenance of reduced limb circumference, especially in secondary lymphedema	Yasuhara H *et al.* 1996 [55]

defined.[25-27] Much of the current evidence offers descriptive studies in narrowly focused disease-specific populations such as chronic venous insufficiency and lymphoedema, rather than focusing on the larger construct of treating edema.[25, 28] Few trials have assessed compression modalities

in conjunction with other therapies such as mobility, decongestive lymphatic therapy (DLT) or skin hygiene.[29-31] Further, even fewer trials have compared different compression modalities between and within the edema population. Table II highlights compression studies that demonstrate the positive outcomes through the utilization of compression therapy. Clinical compression applications must also be assessed to determine their feasibility, clinical utility and most importantly acceptability to the patient.[32-55]

Inadequate, disparate and even conflicting recommendations are presented in the literature. Compression therapy applications are known to be effective in promoting wound healing with venous insufficiency; however clinical guidelines for compression application are not evident in review studies.[35-37] In healthy individuals and in early stage venous insufficiency lower levels of compression improve patient-reported symptoms.[38-42] Chronic venous edema is reduced by compression in a dose-response relationship with higher levels of compression demonstrating greater effect.[43] However, this relationship is not seen in the upper extremities.[44]

Compression effectively reduces edema in acute proximal deep vein thrombosis [30, 45] and can prevent post thrombotic syndrome.[46-52] Other unique swelling conditions such as lipoedema, postsurgical edema and traumatic edema respond to compression but parameters for compression interventions remain ill-defined.

Studies of compression in lymphoedema focus primarily on volume reduction and demonstrate the effectiveness of compression modalities.[53] Volume loss under inelastic compression bandages in the legs correlates with the fall of the bandage pressure starting immediately after application of the bandage suggesting efficacy of short-stretch inelastic compression for leg edema.[54] While it is reasonable to study limb volume reduction as a primary outcome variable to demonstrate efficacy of compression, volume reduction does not absolutely correlate with improved quality of life, mobility status or functional abilities.The following three domains characterizing the functioning of a patient need to be taken into consideration: 1) the domain of physical function and structure (strength, motion, weight, volume, etc.); 2) the domain of activity (waking, functioning as a person, activities of daily living) and 3) the domain of social participation (work, sports, etc.).[33, 34, 55-57] Evidence is lacking to assess the impact of compression therapy on quality of life (QOL) and functional mobility.

Compression therapy in chronic edema management

Compression therapy is a mainstay of treating chronic edema. External application of pressure against the tissue aids in reducing fluid filtration from the blood and further promotes fluid reabsorption into the venous (transiently) and lymphatic circulation.[12, 13] Compression devices harness the force of the muscle pump resulting in increased frequency and amplitude of lymph collector contractions.[58-60] Further, a down-regulation of proinflammatory cytokines has been identified with consistent compression therapy and overall fluid volume decongestion.[61-63]

Compression interventions will remove fluid congestion from the tissues however, compression therapy does not fully evacuate the protein concentration in the interstitium.[12, 64] With residual elevated protein concentrations, oncotic tissue pressure in the interstitium remains elevated and may perpetuate additional swelling. Therefore, compression becomes a long-term need, necessary to prevent refilling of edema into the tissue spaces.

Many compression devices and modalities exist for managing swollen limbs including compression garments and stockings, inelastic compression bandages and intermittent pneumatic pumps. These modalities are effective when applied at a specific frequency and duration by a knowledgeable clinician (Figure 1).

Compression hosiery

The main indication for compression hosiery is long-term management of chronic edema in the initial treatment or maintenance therapy phases. Hosiery may be indicated for prophylaxis in patient groups at high risk for developing edema.[65, 66] Hosiery may not be the optimal compression intervention during the decongestive treatment phase as a more dynamic, adjustable modality is needed to accommodate the changing limb particularly if the limb is misshapen. However,

in an effort to preserve resources, some centers accommodate gradually decreasing limb volume by continually adapting the garment using sewing machines.[67] This is only advisable under conditions where the revisions can be closely supervised. An alternative approach to accommodate limb volume reduction is to order new stockings in progressively decreasing sizes as the limb decongests. This may be adequate for smaller limbs that only require one modification in size, but can be resource intensive with considerable limb decongestion.

Compression hosiery use must be considered in its entirety in clinical trials. Special considerations include; garment pressure, stiffness, type of weave, comfort level, ease of use, patient buy-in, functional considerations and perceptions. These are all potential barriers to wear and compliance with compression hosiery. However, when these factors are considered and efforts are made to positively impact them outcomes are improved as is patient compliance and satisfaction.[23]

Compression bandages

Treating severe forms of chronic edema requires multi-layer compression bandaging. The bandage complex is composed of various materials applied in overlapping layers with consistent tension and methodology.[68, 69] Pressure is generated against the limb based on the level of tension in the bandage layer, the radius of the limb and the elastic properties of the materials applied. The inherent need to individualize the bandage complex makes comparability and extrapolability between different bandages systems difficult. In the context of clinical trials, a common nomenclature and commonly used mechanisms of measuring pressure across different bandage applications is recommended. The ICC, in a past consensus document, proposed a simple and consistant mnemonic scheme to compare different types of compression applications. This is the P-La-C-E system:[69]

P: pressure exerted when the bandage is applied;

La: the number of layers applied;

C: components used in the bandage complex;

E: elastic property of the single component.

The pressure, measured at the distal lower leg can be mild (>20 mmHg), moderate (20-40 mmHg), strong (40-60 mmHg) or very strong (>60 mmHg).[69] It will depend on the tension during application, the radius of the limb segment and on the amount of layers applied. Varying the materials used in the bandage complex (*e.g.*, protection padding, foam layering etc.) influence the pressure, stiffness and overall performance of the final bandage.[70]

When bandages are used in a trial it is advisable to describe these four main criteria when defining the nature of the compression bandage complex applied to the limb. The most important parameter defining the "dosage" of compression therapy is certainly the exerted pressure of a bandage which always should be measured.[71]

Pneumatic compression devices

Intermittent pneumatic compression (IPC) devices are effective when used as part of multi-modality therapy. Trials for optimal use are ill-defined [25, 27] but some remedies of chronic edema can be anticipated when using IPCs for chronic venous edema, and lymphoedema. IPC use is also indicated with immobile patients in whom the pneumatic device provides a rhythmic massaging that can partly substitute for the lacking muscle pump activity.[72] IPC enhances arterial flow and can also be safely and effectively used in patients with arterial disease.[73]

Clinical trial constructs and methodology

Compression efficacy trials require a general standardized method for measuring meaningful change in the limb over time. Protocol standardization, regardless of the chosen study construct, is paramount to assuring valid outcomes. The study must be powered appropriately based on the population and select variables. A washout period of 2-3 weeks is recommended prior to patient enrollment in any edema trial to negate potential bias that may be introduced by acute conditions or other ongoing treatment modalities.

Measures should be standardized and completed at defined periods of time, in an ongoing interval fashion. Serial measures are preferable to pre-intervention/post-intervention measures,

as the measured change over time contributes to understanding the effectiveness of compression interventions, the rate of decongestion over time, changes in the interface pressure and concomitant functional gains. The final assessment comparing compression devices should consider change of the outcome variable using a clearly defined time and measurement units. These meaningful variables enhance the ability to extrapolate trial results to a clinical setting. Blinded methodology is recommended for data entry to reduce measurer bias. Further, efforts should be made to document the time of day when all measurements are taken.

Clinical trials should optimally follow a cohort over an extended period of time. For example, the current criteria of the Cochrane group suggest that clinical trials run a minimum of 24 months in duration to optimally reduce bias in a systematic review.[74] However, to assess the efficacy of compression therapy between different devices and various materials outcome data obtained over shorter time periods is worth while.

Measurement of edema

Volumetric assessment

Full limb volumetric assessment is necessary to quantify edema volume and to monitor change over time. A valid tool is necessary, but one that also has good clinical utility is preferable.[75] Regardless of the measurement tool standardization of the methodology is of paramount importance. The measurement technique of choice must also demonstrate clinical efficiency and be amenable to the patient. In patients with unilateral swelling the amount of edema can be determined by assessing full limb volume of both extremities and comparing the difference between the two. The unaffected contralateral limb then serves as a control mechanism enabling quantification of change in limb volume that is associated with normal anthropometric body changes as opposed to volume reduction. When edema involves both legs limb volume should be quantified for each leg independently. Meaningful change measured after a short time period of compression is a valid measure for volume reduction.

Water displacement techniques as originally described by Archimedes are a notable gold standard for measuring limb volume.[76, 77] However, in regards to measuring lower limb volume, water displacement is clinically complicated; as assessing the full limb is quite difficult and depends on the agility of the patient and in some instances a very large volumetry tank. Further, hygienic issues are complicated with a fluid-filled water tank used widely in a clinical setting.

Circumferential girth measurements are repeatable and reliable measures [77-80] taken at standard intervals along the limb.[79-81] The clinical utility and cost effectiveness of this application are apparent.

Optoelectronic infra-red volumetry is a highly sensitive tool for volumetric assessment.[82-85] This imaging technique provides an excellent accurate volume measurement however may be cost prohibitive in smaller clinical settings.

New emerging technologies in limb volume measurement should also be considered in constructing clinical trials. Techniques such as 3-D photography, magnetic resonance imaging (MRI) and multi-slice computed tomography (MSCT) demonstrate early results quite favorable to precise limb volume measurement.[85-87] However, these techniques are expensive and not readily available for use in clinical trials. We recognize and emphasize the importance of incorporating these technologies into ongoing compression trials to further develop their clinical utility in chronic edema measurement.

Multi- or single frequency bioelectrical impedance may be used to assess the composition of tissue and distribution of body fluids. Bioimpedance measures may be useful in monitoring early changes in limb volume over time and can be used reliably in unilateral or bilateral cases.[88-92] However, a clear quantification of this measure remains clinically complicated.

The body of evidence supporting the validity of these techniques is robust;[64, 67, 76-79] however, specific methodology must be drawn from the appropriate literature that validates these measures in lower limb edema.

Tissue assessment

Quantifying the biomechanical properties of tissue is important in the context of changing

TABLE III.—*Patient characteristics.*

- Age
- Medical comorbidities (hypertension, diabetes, etc.)
- Lab values (blood counts)
- Body mass index
- Affected side (right/left)
- Sensory integrity
- Presence of venous disease
- Degrees of range of motion (hip, knee, ankle)
- Time course of symptoms/condition
- Lymphedema ISL- stage: 0 - III
- Segmental deformities and edema distribution
- Baseline absolute volume (mL) for each limb
- Baseline volume differential (mL)
- Baseline pain in affected limb – Visual Analog Scale (VAS)
- Baseline heaviness - VAS
- Pitting test
- Presence of fibrosis
- History of infection of the affected limb
- Number of previous infection episodes
- Type of surgery
- Presence of skin changes
- Ankle/Brachial Index
- Prior deep vein thrombosis

limb volume as it contributes to an understanding of changes in the cellular matrix of the tissue. Trials that incorporate this methodology may consider; composition of the skin, skin fold thickness, ultrasound indentometry, tonometry, durometry, and skin temperature changes.[93-95] Assessing the degree of fibrosis or scarring in the soft tissue is clinically useful in determining the appropriate choice and efficacy of compression modalities. Skin temperature elevation and a reduced inflammatory process are observed during effective compression with short stretch, multi-layer bandaging.[61] These changes should be quantified during compression therapy trials to provide insight to selecting the best compression application for the patient based on their tissue properties.

Pressure and stiffness measurement of compression materials

Interface pressure should be measured at the medial aspect of the distal leg. Optimal pressure measures are done at the transition between the muscular and tendinous junction of the gastrocnemuis muscle after application and before removing the compression device.[71] The exact position of additional measuring probes may be standardized at points along the medial aspect of the limb as suggested by the German institute for quality control of compression garments.[96]

TABLE IV.—*Primary outcome variables.*

- Subjective symptoms
  - Global rating visual analog scale (VAS)
  - Pain VAS
- General and disease specific quality of life (QOL) measures
  - Quality of life for limb lymphedema
  - FLQA-I
  - Short form - 36
- Disability specific outcomes measures
  - World Health Organization Disability Assessment Scale (WHODAS)
  - Berg balance test
  - 6 minute walk test
- Interface pressure of compression device
- Compliance with compression devices
- Comfort
- Cost
- Volume
  - Total edema limb volume
  - Volume differential between limbs
  - Volume change over time
- Skin temperature
- Range of motion (ROM)
- Muscle strength
- Tissue changes
  - Durometry
  - Tonometry
  - Ultrasound indentometry
  - Pitting
- Anthropometric measures
  - Weight
  - Body Mass Index
- Skin assessment
  - Skin folds
  - Skin change

Measures are taken at rest but also during exercise and mobility to assess the garments response to stretch over time. This enables quantification of the compression products stiffness properties.[71] Standardization of position and activity must be assured and it is advisable to use the same device for all repeated measures between and within patients.

Meaningful clinical change and functional outcomes

In clinical practice the question is raised: How vitally important is the quantity of limb volume reduction in determining meaningful improvement? Volume change measured with a valid tool is a relevant objective parameter to assess compression efficacy, but consideration must also be given to the patients functional outcomes. Limb volume improvement alone may not positively impact the

patient's quality of life or their functional status. Trials are challenged to capture characteristics (Table III) and incorporate measures that reflect overall improvements in the patients physical function and quality of life [97] (Table IV).

In clinical domains, patients complain of pain, discomfort with mobility, joint discomfort, and limited tolerance to activities due to a large oedematous limb. Ill-fit or excessively cumbersome compression modalities also exacerbate these complaints. The psychological stresses associated with the unfavorable cosmesis of the limb also impact patient function. Even without maximal volume decongestion, meaningful clinical change can be experienced in the functional and psychological domains.[34] The importance of these factors must not be diminished.Trials should include measurement tools to gauge the comfort of the compression garment and the subjects reported compliance with compression wear. Studies that capture information regarding physical, recreational and social activities will inform the evidence-base regarding the more functional and practical aspects of compression use.[34, 56, 57, 97]

Good clinical practice

The formal requirements from good clinical practice (GCP) recommendations, based on the Helsinki declaration, must be fulfilled. This also includes the agreement of a local ethics committee.[98, 99] Trial registration in the International Standard Randomised Controlled Trial (ISRCTN) register or with the United States National Institutes of Health Clinical Trial registry is recommended. Adherence to checklists formulated by such groups as CONSORT and SIGN 50 may improve the methodology and reporting of future clincal trials and practice guidelines.[100-103]

Subject inclusion/exclusion criteria

Subject selection and stratification should be clearly defined and enable the widest variability in underlying disease populations within the study construct. Large scale trials with subjects of mixed origins of edema will enable greater ability to extrapolate findings to other populations.

The inclusion criteria should enable the broadest representation of patients with chronic edema. Variables regarding treatment interventions, patient characteristics, demographic information and comorbidities as well as additional objective and self-reported outcomes should be captured (Tables III, IV) These variables contribute richly to the profile of the patient who develops chonic edema and may inform us as to who will respond to certain treatment interventions. Further they enable researchers to draw conclusions about the patients' functional, social and psychological domains as they relate to chronic edema and its management. Every effort should be made to include subjects of various racial and ethnic backgrounds. Exclusion from study participation is recommended for conditions that may skew results (Table V).

TABLE V.—*Exclusion criteria.*

- Anticipated short life-span of the patient
- Traumatic injury or surgery during the study period
- Clinical manifestation of infection at enrollment
- Acute venous thrombosis or phlebitis
- Decompensated heart failure
- Severe pulmonary insufficiency
- Active and clinically significant liver or renal disease
- Contact allergies relevant to compression materials (latex)
- Serious psychiatric disorders (severe depression etc.)
- Significant mental delay that prevents comprehension/learning
- Severe peripheral arterial occlusive disease (ABI<0.5)

Drop-out and adverse events

A report of informed consent is necessary and all trials are voluntary for patients. The reason for a discontinuation of the study shall be specified. Adverse events of particular interest to patients with lymphoedema include; acute inflammatory episodes, erysipelas, rapid volume increase, skin breakdown (rashes), blood clots and recurrent cancer.[103- 105] Events need to be documented and each investigator will make individual decisions about whether the subject continues in the trial

Clinical trial proposals

The authors offer specific recommendations for future compression therapy clinical trials.

These recommendations are outlined in Appendix 1. This research agenda is intended to guide researchers towards a cohesive effort to remedy deficits in the literature. Collaborative global efforts should be made in undertaking these trials to enable results that transcend national boarders. Study results should aim to inform best practice, but will also be useful in contributing to policy and payment structures. Large studies conducting cost analyses and cost-effectiveness comparisons can directly impact policy regarding delivery of services, access to materials and interventions and payment for services.

Conclusions

Clinical trials are needed to assess the efficacy of compression therapy in managing chronic edema of the lower extremities. This document outlines proposed variables and methodology for conducting necessary clinical trials according to gaps evident in the current literature. Researchers and industry efforts for collaboration should be optimized as trial constructs are developed and carried out.

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Appendix I

Recommendations for compression therapy trials in lower extremity chronic edema.

Compression Trials related to decongestive lymphatic therapy (DLT)

Therapeutic trials

- DLT ± Intermittent pneumatic compression (IPC)
- DLT groups randomized:
    - Compression bandaging (CB) *vs.* IPC
    - CB *vs.* Compression stockings
    - CB *vs.* Compression stockings of progressively smaller sizes throughout trial
    - CB *vs.* IPC *vs.* alternative compression devices
- DLT maintenance – conducted after completion of intensive therapy and monitored over time
    - Garment wear *vs.* bandaging and garment wear
    - Garment wear *vs.* IPC and garment

Compression trials

- Comparison of bandaging materials and systems
    - Comparing frequency and duration of application
    - Comparing use of different materials
    - Comparing various pressure levels on same stage of swelling
    - Comparing various levels of stiffness on same stage of swelling

Compression trials related to intermittent pneumatic compression*

- IPC alone *vs.* IPC with garment use
- IPC alone *vs.* IPC with mobility exercises
- IPC in immobile patients

*Swelling of similar stages randomized to different compression levels

Materials trials

- Interface pressure change over time during compression wear
- Skin temperature changes over time during compression wear
- Patient comfort and compliance
    - Between different compression systems
    - Within the same compression system
    - Multi-layer CB *vs.* other materials
    - Multi-layer stockings *vs.* CB *vs.* other materials

- Comparison of compression hosiery of varying levels of stiffness
- Assess changes in tissue density (fibrosis) with various compression devices

Compression in immobile patients
- Comparison of various levels of compression
- Comparison of materials

Interface pressure trials
- Time course
    - o Changes over time with continued compression wear
    - o Reapplication of CB at specified pressure threshold *vs.* no reapplication
    - o Impact on tissue density (fibrosis)

Quality of life trials:
- Assess functional changes and quality of life
    - o volume reduction
    - o maintenance of limb volume
    - o within and between various types of compression devices
- Assess adherence
    - o IPC *vs.* CB
    - o CB *vs.* Stocking wear
    - o CB with padding *vs.* CB w/out padding

Computer simulated compression trials [105]
- Correlate tissue volume decrease with compression levels
- Compute compression level required to prevent swelling of body region in relation to capillary pressure and lymphatic drainage impairment
- Compute level of compression needed to prevent swelling in various body regions
- Efficacy increases non-linearly with compression (suggesting a threshold)
- Simulate working and resting pressures at different levels of compression on different areas of the limb

Simulate effects of changing capillary pressure

Cost effectiveness trials
- Compression bandaging (CB) *vs.* IPC
- CB *vs.* Compression stockings
- CB *vs.* Compression stockings of progressively smaller sizes throughout trial
- CB *vs.* IPC *vs.* alternative compression devices

Epidemiology of compression use
- Within country and between country use of compression devices
- Compression use within various disease states

Variability of compression pressure
- Intra- and inter-therapist bandaging with similar and different materials