

TRATAMENTO MÉDICO DO LINFEDEMA DOS MEMBROS INFERIORES

NON-SURGICAL TREATMENTS OF LYMPHEDEMA OF THE LOWER LIMBS

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RESUMO

Introdução: O linfedema dos membros inferiores é caracterizado pela acumulação de líquido intersticial rico em proteínas consequente a uma insuficiência do sistema linfático, resultando em edema progressivo e não depressível do membro inferior. Há 2 tipos de linfedema primário e secundário. O primeiro sem etiologia conhecida. O diagnóstico é feito através da avaliação clínica em combinação com modalidades de imagem. O tratamento médico do linfedema dos membros inferiores é baseado em medidas preventivas, alterações do estilo de vida e modalidades de compressão contínuas, com o objetivo de reduzir a congestão do edema e melhorar a qualidade de vida dos doentes.

Objetivos: A presente revisão literária tem como objetivo compilar o conhecimento científico atual acerca dos diversos domínios do tratamento médico do linfedema dos membros inferiores.

Metodologia: A pesquisa foi realizada na base de dados do PubMed, utilizando os seguintes termos médicos (MeSH): “lymphedema”, “lower limbs” e “medical treatment”. Foram selecionados artigos de investigação e de revisão indexados nos últimos 10 anos e escritos em inglês. Os projetos de experimentação animal e relatos de caso clínico isolado foram excluídos. Outros materiais pesquisados incluíram livros de referência na área de Cirurgia Vascular, nomeadamente Rutherford Vascular Surgery – 9ª Edição, 2018.

Desenvolvimento: O tratamento médico do linfedema dos membros inferiores é caracterizado por uma abordagem multifacetada, que inclui a redução mecânica do edema dos membros, dispositivos médicos alternativos e terapia farmacológica. A terapia descongestiva complexa é considerada o tratamento padrão e suas modalidades de compressão incluem massagens manuais de drenagem, compressão pneumática, sistemas de bandagem, vestuário de compressão e exercício físico. As terapias de compressão diferem no grau e tempo de pressão aplicados e podem ser administradas por profissionais de saúde ou pelo próprio doente. A duração das fases do tratamento é variável e este pode incluir regimes hospitalares e em ambulatório. Os resultados positivos do tratamento incluem o aumento da elasticidade da pele, a diminuição do volume do membro, a redução da dor, o aumento da capacidade funcional e a melhoria da qualidade de vida.

Conclusões: As modalidades de compressão demonstraram ser eficazes na redução do volume dos membros, aumentando a elasticidade dos tecidos e melhorando os aspetos físicos, psicológicos e estéticos da vida do doente. No entanto, a manutenção das reduções de volume dependem principalmente da aderência ao tratamento por parte do doente. As abordagens intensivas e em regime de ambulatório não comprometem a eficácia do tratamento e as terapias de alta pressão são eficazes e bem toleradas. O atual tratamento médico do linfedema carece de resultados a longo prazo e necessita de alternativas terapêuticas mais eficazes.

Palavras-chave

Linfedema, membros inferiores, tratamento médico

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ABSTRACT

Background: LLL is characterized by protein-rich interstitial fluid accumulation due to lymphatic system insufficiency, resulting in progressive non-pitting edema. Primary and secondary lymphedema are distinguished by the absence or presence of an external triggering factor, respectively. Diagnosis is based on clinical examination combined with imaging modalities. The non-surgical approach of LLL is based on preventive measures, lifestyle interventions and life-long compression modalities, aiming to reduce the edema congestion and to improve patient quality of life.

Objectives: The present literature review aims to compile current scientific knowledge on the various domains of the non-surgical treatments of LLL.

Methods: Search was performed in PubMed database, using the following medical subjects heading (MeSH) terms: "lymphedema", "lower limbs" and "medical treatment". Research and review articles indexed in the last 10 years and written in English language were selected. Animal experimentation works and single case-reports were excluded. Other materials searched comprised reference books in the area of Vascular Surgery, namely Rutherford Vascular Surgery – 9th Edition, 2018.

Development: The non-surgical treatment of LLL is characterized by a multifaceted approach, including mechanical reduction of limb swelling, alternative medical devices and pharmacological therapy. Complex decongestive therapy is recognized as the standard of treatment and its compression modalities include drainage massages, pneumatic compression, bandaging systems, compression garments and physical exercise. Compression therapies differ in the degree and time of pressure applied and can be performed by healthcare professionals or by the patient himself. The duration of treatment stages varies and it may include hospital and outpatient regimens. Positive treatment outcomes include increased skin elasticity, limb volume reduction, pain relief, increased functional capacity and improved quality of life.

Conclusions: Compression modalities have been shown to be effective in reducing limb volume, increasing tissue elasticity and improving the physical, psychological and aesthetic aspects of patient life. However, sustained volume reductions depend mostly on patient diligence. Intensive and outpatients approaches do not compromise treatment efficacy and high pressures therapies are effective and well tolerated. Current lymphedema non-surgical treatment lacks long-term results and urges more effective therapeutic alternatives.

Keywords

lymphedema, lower limbs, medical treatment

BACKGROUND

Lymphedema is a progressive non-pitting edema⁽¹⁾ characterized by protein-rich interstitial fluid accumulation secondary to lymphatic insufficiency,⁽²⁾ presenting increased tissue fluid, fibrosis, adipose hypertrophy, inflammation and pathological lymphangiogenesis.⁽³⁾

The primary form is characterized by intrinsic abnormalities in the development of lymphatic vasculature,⁽⁴⁾ while secondary lymphedema occurs in response to an external triggering factor.

⁽⁴⁾ Primary lymphedema has been associated with mutations in several genes, including VEGFR3 (Milroy's disease), FOXC2 (lymphedema-distichiasis) and SOX18 (hypotrichosis-lymphedema-telangiectasia syndrome). The causal gene determines disease phenotype, lymphedema mechanism and age of onset, from which it is classified in congenital, praecox (pubertal) and tarda.⁽⁵⁾ Therefore, the specific genotype will have implications on lymphedema best approach.⁽⁶⁾

Lower limb lymphedema (LLL) affects around 6 million people worldwide.^(7,8) Filariasis and cancer-related lymphedema are the most prevalent forms in undeveloped countries and in the industrialized world, respectively.^(4,9)

Lower limb swelling induces symptoms of tightness, pain, heaviness, redness, restricted movement and skin thickening, which are precipitated or exacerbated by long periods of standing, walking, sitting and heat.⁽¹⁰⁾ Lymphedema unique characteristics include "peau d'orange" and a positive Stemmer sign.⁽¹¹⁾ Clinical categorization is based on the International Society of Lymphology (ISL) classification⁽¹²⁾ and Common Terminology Criteria for Adverse Events v3.0.⁽¹³⁾ Lymphedema complications comprise secondary infections, including lymphangitis or cellulitis^(14,15) and neoplastic processes, such as lymphangiosarcoma and angiosarcoma.⁽²⁾ Diagnostic methods include tape measurement⁽¹⁶⁾, lymphoscintigraphy,⁽¹⁷⁾ near infrared fluorescence imaging,⁽¹⁸⁾ magnetic resonance lymphangiography⁽¹⁶⁾ and bioimpedance.⁽¹⁹⁾

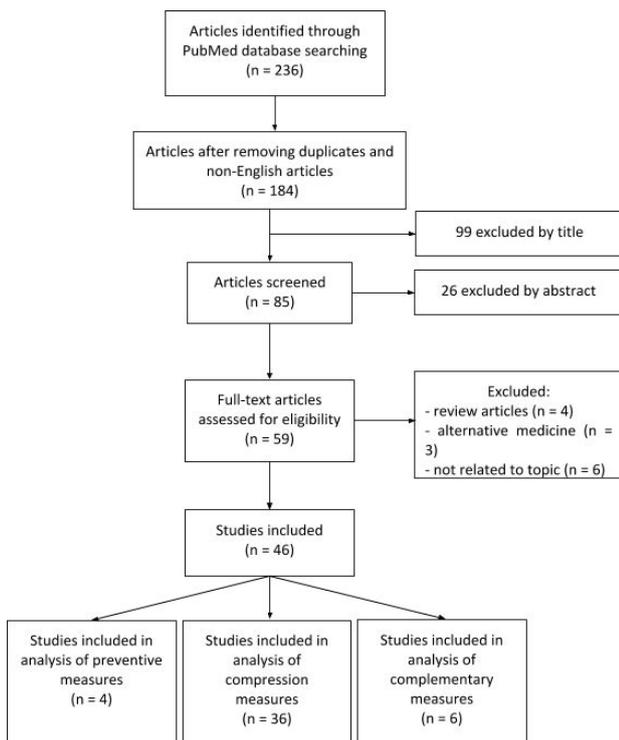


LLL proved to negatively impact patients quality of life⁽²⁰⁾ and degrees of productivity.⁽⁷⁾

Lymphedema integrated treatment include non-surgical and surgical approaches, though not healing the underlying disease process. Classical physiotherapeutic techniques include drainage massages, pneumatic devices, compression bandages and hosiery. The present literature review aims to compile current scientific knowledge on the various domains of the non-surgical treatment of LLL.

METHODS

Search was performed in PubMed database, using the following medical subjects heading (MeSH) terms: "lymphedema", "lower limbs" and "medical treatment". Research and review articles indexed between January 2009 and December 2018 and written in English language were selected. Animal experimentation works and single case-reports were excluded. Other materials searched comprised reference books in the area of Vascular Surgery, namely Rutherford Vascular Surgery – 9th Edition, 2018.



RESULTS

Therapy is designed regarding lymphedema stage and origin and patient functional status, ability to perform self-management and risk reduction potential.⁽²¹⁾ Surgical approaches are mostly reserved for severe lymphedema non-responder to conservative measures.⁽²²⁾ Non-surgical treatment of lymphedema is divided into two main categories: primary preventive measures and interventions for those with established disease,

mainly focused in reducing edema, preventing skin infection and minimizing functional loss.⁽²⁾

Target therapies have been emerging to combat the lack of efficacy of the recent approaches, aiming to reverse lymphedema fundamental pathophysiology, such as mesenchymal stem cell and vascular endothelial growth factor-C therapies.^(24, 25)

Preventive Treatment and Lifestyle Interventions

Monitoring fluids ingestion and reducing salt intake are often recommended,⁽²⁾ but failed to prove impact on lymphedema severity.⁽¹¹⁾ Other preventive measures include skin and nail care, weight loss, aerobic exercise, limb elevation, trauma and extreme temperatures avoidance.^(2, 26) Avoidance of air travel and venipuncture and compression on the affected limb are some additional preventive measures supported by limited scientific evidence.⁽²⁷⁾ In filariasis endemic areas, transmission is interrupted by the implementation of mass drug administration with ivermectin or diethylcarbamazine citrate (DEC) in association with albendazole.⁽²⁹⁾ Recent results point to the additional role of DEC and albendazole in reversing lymphatic pathology of both symptomatic and asymptomatic pediatric population.⁽³⁰⁾

In developed countries, preventive measures include minimal invasive oncologic surgeries and prompt resolution of the recurrent infections events.⁽²⁾ Antibiotic prophylaxis should be considered in patients who have recurrent cellulitis using phenoxymethylpenicillin or cephalexin as first choice. Alternatives for patients allergic to penicillin include erythromycin and clarithromycin.⁽²⁸⁾

Mechanical Decongestive Lymphatic Therapy

Compression is the cornerstone of mechanical decongestive lymphatic therapy (MDCT)⁽³¹⁾ and its effects depend on tissue compliance and edema volume.⁽³²⁾

Contraindications to compression therapy include decompensated cardiac failure, deep vein thrombosis and an ankle-brachial index (ABI) of 0.5 or less.⁽³⁵⁾

External compression modalities include drainage techniques, such as manual massages or pneumatic compression, and contention measures, namely bandaging systems and compression hosiery.⁽²⁶⁾ Treatment design should be based on individual leg shape and edema fluctuations.⁽³⁵⁾

Adjuvant thermotherapy failed to prove synergic effect and even revealed a tendency to compromise the limb volume reductions.⁽³⁶⁾ Nevertheless, compression therapy proved to be optimized by water and vacuum effect.^(37, 38)

Complex Decongestive Therapy (CDT) is recognized as the standard of lymphedema treatment⁽³⁹⁾ and is usually structured in two main phases.^(2, 40) The first intensive treatment phase aims to achieve maximal decongestion and is usually guided by qualified therapists who perform manual lymphatic drainage (MLD), short-stretch bandaging, remedial exercises and dermatological care.⁽⁴⁰⁾ The home-care maintenance phase requires patient instruction and includes the alternating use of low-stretch elastic stocking with multi-layered bandages, skin care and continued exercises,⁽⁴⁰⁾ according to patient individual needs.⁽⁴¹⁾

Volume changes occur primarily within the first phase⁽³⁹⁾ and transition to the second stage occurs after limb volume stabilization.⁽⁴⁰⁾ Therapists-guided management proved to be more effective and only a minority of patients sustain the minimum volume achieved.⁽⁴⁰⁾ The inclusion of the first phase increases patient adherence, establishes more concrete objectives, enables more appropriate management of complications⁽⁴⁰⁾ and quickly restores patient ability to work,⁽⁴²⁾ but failed to significantly impact long-term volume reductions.⁽⁴⁰⁾ Largest volume reductions were seen soon

after the start of the therapy and edema reached its plateau on an average of 5.0 days, favoring the possibility of shortening treatments and potentially reducing their economic burden.⁽⁴³⁾ No additional volume reduction was provided by the in-hospital management when compared to an outpatient therapy, with self-treatment instructions.⁽⁴⁰⁾ Nevertheless, cases of malignant etiology, infants, lymphorrhea and complicated lymphedema should be firstly managed by an in-patient regimen.⁽⁴⁴⁾

Table I Mechanical decongestive treatment protocols

Author	Cohort (n)	Lymphedema characteristics	Treatment protocol
Noh et al. ⁽³⁹⁾	84	Unilateral; secondary upper limb lymphedema; primary and secondary LLL; mild-moderate.	Two-phase treatment: - 2 weeks: 10 sessions of MLD (60 minutes) followed by sequential PCT (30 minutes) with inelastic compression bandaging; - 3 months: self-administered treatments with compression garments. Subjects were instructed about proper self-measures. Daily massages, exercises and skin care were recommended during the all trial.
Hwang et al. ⁽⁴⁷⁾	22	Unilateral upper and lower limb malignant lymphedema.	2 weeks (5 sessions each, guided by a physical therapist): - non-elastic bandage compression; - remedial exercises; - skin care. No sessions of MLD. Drugs for cancer treatment and pain were maintained.
Yamamoto et al. ⁽⁴³⁾	83	Unilateral secondary upper and LLL, stage II.*	Two-phase treatment: - phase I: daily sessions (60 minutes) – MLD, remedial exercises and skin care with multiple layer compression bandaging; - phase II: treatment continuation with compression garments. Transition to phase II occurred after limb volume stabilization.
Pereira de Godoy et al. ⁽⁹¹⁾	33	Primary and secondary LLL, stage III.*	Intensive therapy (5 days): - 8 hours/day: mechanical lymphatic drainage thought plantar flexion and extension; - 15 minutes/day: cervical stimulation; - grosgrain compression stocking alternated with elastic bandages.
Kim et al. ⁽⁹²⁾	158	Unilateral secondary lower-limb lymphedema, stage II-III.*	Two-phase treatment: - phase I (2 weeks; 5 sessions each; guided by physical therapists): manual lymphatic drainage (1 hour), multilayered low-stretch compression bandages with remedial exercises; - phase II (daily sessions): self-administered MLD, skin care and exercise; daily compression stocking and night self-bandaging (3x/week).
Niimi et al. ⁽⁴⁶⁾	207	Unilateral LLL, stage I-III.*	- In-home therapy: compression stocking (morning-bedtime; 30-40 mmHg – mild cases, 40-50 mmHg – advanced cases). - In-hospital therapy (1 week of subjects instruction): low-stretch multi-layered self-bandaging and compression garment. - Both therapies: self-MLD, skin care, leg elevation and exercise under restrain measures.
Stanisic et al. ⁽⁴²⁾	72	Primary and secondary LLL, stage III.*	- Intensive treatment phase (3-6 weeks; daily sessions): MLD, bandaging, motor rehabilitation, pharmacotherapy and skin care; - Maintenance phase: massages (1x/week or 2x/week) and daily custom-made compression hosiery.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL); LLL – Lower Limb Lymphedema; MLD – Manual Lymphatic Drainage; PCT – Pneumatic Compression Therapy.



Shortened and outpatient intensive approaches provided significant improvement in elephantiasis, proving to be an appropriate option for all LLL types.^(45, 46)

Malignant lymphedema can be effectively managed by CDT without MDL, that is thought to stimulate cancer spread.⁽⁴⁷⁾ Numerous CDT treatment protocols have been proved to be an effective treatment in LLL patients, enabling significant limb volume reductions (13.8%-73.5%), with greater changes in severe lymphedema cases.^(39, 42, 43, 47, 48) (Table I)

Outcome predictors of MDLT

The stone-paved ultrasonography appearance was associated with greater absolute volume reduction, while hyperechogenic subcutis predicted worse results.⁽⁴⁶⁾

Subjective impact of MDLT

Compression therapy proved to significantly improve the physical and mental components of patients quality of life (QoL),^(47, 49) also reducing the heaviness feeling, with positive psychological impact provided by the inclusion of exercise protocols.⁽⁵⁰⁾

Leg involvement presented lower pre-CDT QoL levels, than upper extremity lymphedema patients, with higher improvements after CDT, despite similar volume reductions,⁽³⁹⁾ which was mostly due to reduction of deformity, improvement in limb function and joint motion, regression of trophic changes and the possibility of wearing a greater variety of footwear and clothing.⁽⁴⁶⁾

Active treatment of malignant forms resulted in marked physical improvement and significant pain reductions.⁽⁴⁷⁾ Non-painful compression induced analgesia shares similar mechanisms to conditioned pain modulation with contribution of spatial summation.⁽⁵¹⁾

Manual Lymphatic Drainage

MDL applies gentle pressure to the skin, rerouting the fluid to proximal areas and softening the skin.⁽²⁾ It is particularly relevant for body regions which are contraindicated to sustained pressures and should not be prescribed alone for curative purposes.⁽²⁾ Usually, MDL is preceded by manipulations of the proximal areas.⁽²⁾ Drainage techniques, including pumping, scooping and rotary movements, were reported in association with tissue softening maneuvers, with 30 to 60 minutes of massage per leg.⁽⁵²⁾

MDL therapy proved to soften the calf region, although not affecting the thigh level. It revealed a tendency to normalize tissue strains, with two opposite immediate tissue effects, increasing strain in harder tissues and decreasing strain in softer tissues, both presenting correlation between pre-MDL strains and MDL-induced changes.⁽⁵²⁾

PNEUMATIC COMPRESSION THERAPY

Pneumatic Compression Therapy (PCT) is performed by pump garments placed on the affected area, which alternate between inflation and deflation.⁽⁵³⁻⁵⁵⁾

PCT devices differ in the number of chambers, time, pressure, modes of inflation and deflation, pressure gradient and garment design⁽⁵⁴⁾ and are generally easy to operate on a daily-basis.⁽⁵⁶⁾

Pressure and timing of PCT devices are adjustable⁽⁵⁷⁾ and deflation can occur either after total distal to proximal chambers inflation or sequentially after each inflation of the proximal chamber, enabling potential distal displacement of the lymph.⁽⁵⁸⁾

Inflation of the pneumatic chamber proved to induce tissue compression and its partial proximal displacement, whereas deflation caused tissue decompression with recoil to a normal position.⁽³²⁾ Despite the increase in interstitial fluid velocity induced by chamber inflation,⁽⁵⁹⁾ the constant stress may result in decreased flow under its central.⁽⁵⁹⁾

Efficacy of PCT depends on device parameters, but also on tissue features, since fluid accumulation and fibrosis hamper pressure transmission.⁽³²⁾

The ideal pump pressure and its optimal duration is not established,⁽²⁾ thus therapy design should be individualized.⁽¹¹⁾

PCT contraindications include local or proximal malignancy, limb infection, deep vein thrombosis and anticoagulation therapy.⁽⁶⁰⁾

Lymph pathways during PCT

PCT proved to induce contractions of the patent lymphatic vessels and lymph movement towards the proximal limb regions, with both linear and diffuse patterns, suggesting that it occurs through the functional lymphatics and the interstitial channels.^(61, 62) These subcutaneous channels develop in response to fluid accumulation and share no common feature with lymphatic endothelial cells. PCT has proven to replace their missing propelling function and to enhance their formation in proximal limb sites.⁽⁶³⁾

Skin properties and tissue effects during PCT

Stiffness and hydraulic conductivity of tissues are crucial for determining PCT pressure distribution,⁽⁵⁹⁾ and skin dissipations between 40-100 mmHg were reported.^(54, 57, 64)

Chamber inflation revealed limited horizontal transmission of pressure towards proximal non-compressed areas⁽⁵⁴⁾ with increased distal pressures during sequential inflation.⁽⁵⁴⁾

The displaced tissue fluid volumes ranged from 10-40 ml per chamber, being more evident in the thigh.⁽⁵⁴⁾

Similar inflation loads over the pneumatic chambers were associated with an uneven distribution of tissue fluid pressure, with lower levels in the popliteal and upper thigh regions, both containing loose connective tissue and accumulating fluid during external compression.^(54, 64)

PCT usually results in decreased volume of the lower calf and thigh, with increases below the knee and in the upper thigh, evidencing fluid translocations to the popliteal fossa and to the groin region.^(32, 53, 54)

Final improvement usually assumes greater expression in the calf above the ankle and mid-calf, with reported long-term maintenance.^(53, 63) Maximum limb circumference reduction of 94.5% was observed in the foot area, while the thigh region revealed the greatest absolute edema reductions.⁽⁵⁸⁾

Pressure and time setting in PCT devices and clinical outcomes

The level of pressure applied significantly affects PCT outcomes⁽⁸⁾ and effective flow requires tissue fluid pressures above 30 mmHg.⁽⁵⁹⁾

Numerous recent studies point to the efficacy of long timed (>50 seconds) and high pressure (80-120 mmHg)

PCT.^(8, 53, 54, 58, 59, 62, 64, 65) (Table II)

Table II Pressure and time setting in PCT devices and clinical outcomes

Author	Cohort (n)	Lymphedema characteristics	Treatment protocol	Results/Conclusions
Zaleska et al. ⁽⁵³⁾	18	Unilateral LLL, stage II-IV*, duration 3-12 years.	Biocompression pneumatic device set to pressure of 120 mmHg at foot level, with gradual decrease by 20% in the groin. Daily PCT sessions of 45 minutes; 24-36 months.	- Sustained decrease of limb circumference with increased tissue elasticity and no direct correlation between both parameters.
Zaleska et al. ⁽⁶⁴⁾	15	LLL, stage II-IV*, duration 2-12 years.	Biocompression pneumatic device set to 3 inflation times (5, 20 or 50 seconds), with 3 levels of pressure (50, 80 and 120 mmHg).	- Inflation times of 5 and 20 seconds, generated small pressures, mostly below 30 mmHg. - Deflation times of 5 and 20 seconds resulted in maintaining tissue fluid pressures at levels above 20 mmHg. - 50 seconds/chamber was the most favorable timing for both inflation and deflation, with inflation pressures > 30 mmHg, dropping to 0 mmHg over deflation.
Olszewski et al. ⁽⁵⁴⁾	15	LLL, stage II-IV*, duration 2-15 years.	Biocompression pneumatic device set to pressures of 50-120 mmHg, decreasing proximally by 20%.	- High pressures and long compression times were necessary to induce movement of the stagnant fluid.
Olszewski et al. ⁽⁶²⁾	15	Unilateral LLL, stages II-IV*, duration 2-15 years.	Biocompression pneumatic device set to pressures of 50-125 mmHg, decreasing proximally by 10%.	- High pressure sequential PCT is very effective in moving stagnant lymph in cases of obstructive lymphedema, relocating large fluid volumes toward the non-swollen tissues of the groin.
Aldrich et al. ⁽⁶²⁾	4	Unilateral and bilateral; primary and cancer treatment-related LLL, stages I-III*, duration 3-35 years.	Lympha Press Optimal® pneumatic device, set to pressures of 45, 40, 35 and 30 mmHg, decreasing proximally; PCT sessions of 1 hour (60 cycles with 50 seconds each).	- During and after PCT, all of the affected legs revealed increased lymph vessel propulsion, with increased pulsatile velocities and frequencies.
Taradaj et al. ⁽⁸⁾	81	Unilateral and bilateral primary LLL, in association with chronic venous insufficiency, duration 0,6-14,2 years.	4-week outpatient therapy: MLD (50 minutes, 3x/week, guided by physical therapist); multilayered bandaging (40-50 mmHg); pneumatic multi-chambered device set to pressures of 60/120 mmHg (45 minutes, 3x/week); Diosmin (500 mg/day). Control group without PCT.	- High pressure chambers (120 mmHg) had the greatest edema reductions. - Low pressure chambers (60 mmHg) had similar results to control group. - High pressure PCT proved to be effective in reducing phlebolymphedema.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL); MLD – Manual Lymphatic Drainage; PCT – Pneumatic Compression Therapy.



Table II Pressure and time setting in PCT devices and clinical outcomes

Author	Cohort (n)	Lymphedema characteristics	Treatment protocol	Results/Conclusions
Zaleska et al. ⁽³²⁾	20	Unilateral LLL, stages II-IV*, duration 2-15 years.	Two Biocompression pneumatic chambers: control chamber in the ankle (120 mmHg) to prevent back flow; test chamber around the mid-calf sequentially inflated to 50, 80, 100 and 120 mmHg for 1-3 minutes each.	<ul style="list-style-type: none"> - Fluid movement was more evident 3 minutes after the beginning of tissue compression. - Under 120 mmHg of pressure, tissues were still compressible and fluid could be squeezed out. - The effects of chamber inflation depend on the amount of tissue fluid and its degree of fibrosis. - Calf circumference continuously recorded by plethysmography could have a potential role in setting PCT parameters at optimal levels.
Kitayama et al. ⁽⁶⁵⁾	23	Unilateral and bilateral secondary LLL, stages I-II.*	PCT with different modes of inflation (sequential or non-sequential) and deflation (sequential or interrupted); MEDOMER PM-8000 pneumatic device set to pressure of 45 and 90 mmHg, with 30 seconds of inflation and 20 seconds of deflation.	<ul style="list-style-type: none"> - PCT outcomes are affected by its mode of inflation among lymphedema patients. - The sequential mode with distal to proximal inflation prevented the backward flow of lymph and resulted in more effective fluid displacement. - Under the sequential inflation mode, pressures of 90 mmHg achieved higher lymph flow velocities than 45 mmHg. - Sequential programs with high pressure achieved the most favorable results.
Modagheh et al. ⁽⁵⁸⁾	43	Unilateral and bilateral, primary and secondary LLL, duration 1-4 years mostly).	Pneumolymph® pneumatic device set to pressures of 80-120 mmHg, with inflation times of 30 seconds. PCT daily sessions (2 days; 8 hours/day) in an hospital setting.	<ul style="list-style-type: none"> - Unilateral forms of lymphedema achieved a mean edema reduction of 66-94%. - It was found an inverse relation between disease duration and its response to treatment. - Congenital cases revealed poor response to treatment. - High pressures were well tolerated.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL); MLD – Manual Lymphatic Drainage; PCT – Pneumatic Compression Therapy.

COMPRESSION BANDAGING THERAPY

Short-stretch bandages, with limited extensibility between 30-70%,⁽⁶⁶⁾ create cycles between low resting pressures and high working pressures, raising tissues hydrostatic pressure,⁽⁶⁶⁾ mainly in the calf.⁽⁶⁷⁾ Bandaging is usually combined with exercise to optimize its effects.⁽⁴⁶⁾

The inclusion of low stretch bandaging before compression stocking had a significant impact on lymphedema reduction, proving to be a better restrain measure for severe forms.⁽⁴⁶⁾ Bandages should apply a minimum pressure of 40 mmHg in the upright position⁽⁶⁸⁾ and multi-layered and high compression systems are preferable.⁽⁶⁹⁾

Short-stretch compression does not accompany edema reduction and its efficacy can be compromised by non-adequate compression and slippage rates.^(35, 70) Moreover, bandages discomfort and difficult application lead to poor compliance.⁽⁷⁰⁾ Nevertheless, this therapy, including some self-administered techniques,⁽⁴⁶⁾ have revealed positive outcomes, with significant volume reductions, reduced subcutaneous fluid accumulation and improvement in pain and skin thickness.^(46, 70-72) Multi-layer bandaging have proved to be effective as an independent method among elderly lymphedema patients, with similar efficacy to CDT.⁽⁷²⁾

Table III Therapies combined with PCT

Author	Cohort (n)	Lymphedema characteristics	Therapies combined	Results/Conclusions
Zaleska et al. ⁽⁵³⁾	18	Unilateral LLL, stage II-IV*, duration 3-12 years.	- Semi-elastic non-customized compression stockings grade 2, advised by an experienced fitter and changed every 6 months.	- Compression stockings application was associated only with a preventive role in fluid re-accumulation.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL).

COMPRESSION GARMENTS THERAPY

Medical compression garments are usually made of elasticated textile.⁽³³⁾ New prescriptions are required after 3-6 months⁽³³⁾ and skin condition should be monitored.⁽²⁾

Pressures applied vary between 20 and 60 mmHg, decreasing proximally,⁽⁷³⁾ and the highest level tolerated by the patient is considered the most beneficial.⁽³¹⁾ However, lighter medical compression should be considered in some specific conditions, such as ABI values lower than 0.8.⁽³⁵⁾

Pressures of 30-40 mmHg proved to better maintain treatment results than lower garments loads of 20-30 mmHg and further limb volume reduction were achieved with inelastic grosgrain stocking.⁽⁴¹⁾

Compression garments significantly impact long-term maintenance of lymphedema reduction^(31, 41), improving patients

satisfaction with treatment⁽³⁵⁾ and initial prescription of lower pressure stockings may be more effective.⁽⁷⁴⁾

Properly fitted compression stockings add a synergistic effect to mechanical lymph drainage.⁽⁷⁵⁾ Thus, volume reductions of 200-300 mL make adjustment necessary.⁽⁷⁵⁾

Patient in compliant use⁽⁷⁴⁾ (Table IV) is aggravated by potential impaired mobility.⁽⁷⁶⁾ The mean duration of illness was found to be 10 times higher than the average of garment use.⁽⁷⁴⁾ Nevertheless, treatment is accepted by the majority of patients,⁽⁷⁴⁾ with reported high levels of adherence to its prophylactic use.⁽⁷⁶⁾

Daily compression stocking use proved to decrease the incidence of secondary lower limb swelling after lymphadenectomy, improving symptoms and clinical examination, without compromising patients QoL. However, it failed to reduce clinically significant LLL and did not affect the complication rate.⁽⁷⁶⁾

Table IV Factors affecting compression stocking use⁽⁷⁴⁾

	Reasons	Solutions for a better use
Irregular use and discontinuation	- discomfort (tightening); - ablutions impediment; - difficulty of using.	- greater usefulness; - ablutions availability; - greater comfort.
Use and discontinuation	- discomfort (tightening); - overused old stocking; - difficulty of using.	- greater usefulness; - reimbursement of new stocking; - doctors recommendations.
Occasional use	- discomfort (tightening); - difficulty of using; - ablutions impediment.	- greater usefulness; - greater comfort; - ablutions availability.
Continued use	- reduced complains; - doctors recommendations; - improved QoL.	- greater usefulness; - ablutions availability; - different color, model and material.
Not buying	- difficulty of using; - expensiveness; - reported usefulness.	- reduced costs; - being awared of the need to use; - greater comfort.

QoL - Quality of Life.



PHYSICAL EXERCISE THERAPY

Remedial exercises and aerobic workout are part of lymphedema comprehensive approach,⁽²⁾ ranging from cycling high-load exercises to aquatic protocols,^(38,50,77,78) (Table V)
 Exercise effectiveness increases with lymphedema severity⁽⁷⁸⁾

and its positive outcomes include reductions in limb volume and subcutaneous skin thickness and improvements in pain, heaviness, edema status and patients QoL, mainly due to effects in fatigue and physical function. Positive psychological impact and high compliance rates are also reported.^(50,77,78)

Table V Physical exercise protocols

Author	Cohort (n)	Lymphedema characteristics	Exercise protocol	Results/Conclusions
Do et al. ⁽⁷⁷⁾	40	Unilateral, secondary LLL, stage I-III.*	Two-phase treatment: 0-2 week supervised by a physical therapist; 2-4 week at home (daily sessions; 30 minutes). Exercises were performed under compression stocking. Previous 10 CDT sessions (4 weeks).	<ul style="list-style-type: none"> - Improve in edema status, fatigue, pain and QoL. - No significant difference in limb volume. - Patient with advanced stages of LLL can be safely recommended to perform daily exercise at moderate intensity.
Fukushima et al. ⁽⁷⁸⁾	23	Secondary LLL, stage II.*	3 sessions (1-week washout period); compression therapy alone, low-load and high-load active exercise performed using the training mode of Strength ErgoTM240 bicycle ergometer (high-load: 10% intensity; low-load: 5% intensity) and under multi-layered compression bandaging (calf pressures: 40 mmHg).	<ul style="list-style-type: none"> - High-load exercise therapy is more effective in decreasing lower limb volume than compression therapy alone. - High-load exercise is more effective in cases of severe lymphedema. - Improvement in pain, heaviness and pitting edema with the 3 interventions.
Gianesini et al. ⁽⁵⁰⁾	16	Bilateral LLL, with duration >3 months.	Pool at a constant temperature of 33°C. "HydroFE" (5 sessions of 50 minutes, 2/week, guided by hydrotherapeutic personal trainer): cycling-like activity in the supine and standing position; repeated series of tip-toes exercises, hip, knee and ankle flexion-extension; forward and lateral walking.	<ul style="list-style-type: none"> - Limb volume reductions were maintained over time. - Increase in both dorsal and plantar flexion of the ankle. - Decreased skin thickness and limb heaviness. - Positive psychological impact. - Good compliance rates.
Ergin et al. ⁽³⁸⁾	57	Unilateral, primary and secondary LLL.	A 1.4-m deep pool at temperature between 32-33.5°C. 6 weeks of 45-60 minutes sessions, 2x/week, with 5-8 to eight patients in each group: breathing exercises; proximal movements of chest and trunk with self-massage; distal movements involving hips, knees, ankles, and toes with self-massage; remedial exercises proximal to distal; self-management procedures were maintained during the rest of the week.	<ul style="list-style-type: none"> - Decrease in volumetric displacement and limb circumferences. - Improved functional capacity. - Improved quality of life, reduced social anxiety and negative expectancies about future events. - Improvements were higher in the aqua-lymphatic therapy group than in the control physiotherapy group.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL); CDT – Complex Decongestive Therapy; QoL – Quality of Life.

ALTERNATIVE LYMPHEDEMA MEDICAL DEVICES

volume reduction, drainage improvements and increased tissue elasticity, some even enabling its application on a daily-basis,⁽⁸⁰⁻⁸³⁾ (Table VI)

In addition to pneumatic systems, alternative medical devices have been purposed by some authors, promoting sustained

Table VI Alternative Lymphedema Medical Devices

Author	Cohort (n)	Lymphedema characteristics	Device mode of action	Treatment protocol	Results/Conclusions
Elio et al.(81)	8	Unilateral, primary and secondary LLL, stage I-III.*	Trasponder®: - bioresonance microcurrents; - transdermal delivery of magnesium silicate by electroporation.	6 sessions of 45 minutes (0-2 guided by physiotherapist; 3-6 self-administered). Previous use of compression stocking 2 months before (20-30 or 30-40 mmHg).	- Reduction of 2% in limb volume and 21% in the amount of intercellular space fluid. - Fluid changes of 18%. - Improvement of main symptoms and pathologic signs. - High compliance and proven ease of acquisition of self-administered technique. - No side effects.
Cavezzi et al.(80)	8	Unilateral, primary and secondary LLL, stage III.*	Flowave 2TM: - bioresonance microcurrents; - vacuum-suction mechanism.	10 daily sessions (1 hour; guided by physiotherapists). Use of compression stocking one month before and during the trial.	- 5% of improvement in total limb volumetry; more pronounced reduction in lower leg area (8%). - Lymphoscintigraphy parameters: improvement in lymph node uptake (more pronounced in the inguinal than in the popliteal area); improvements in collectors drainage and radioisotope stagnation (more pronounced in the latter images - 45-120°); early improvement in dermal backflow. - High compliance. - No side effects.
Olszewski et al.(82)	5	Unilateral LLL, -duration 2-12 years.	Linforoll: handpiece with a roller-containing pressure wirelessly transmitting the values of applied force to the computer screen, during the rolling cycle; pressures applied of 80-120 mmHg; 25 rollings in each limb area (6/minute).	Daily sessions of 1 hour, during 2 weeks.	- Levels of tissue pressure are 30-50% lower than the applied pressures. - Decrease in limb volume by 6.1-1.5%. - Increase in tissue elasticity. - Increase in proximal limb circumference (proximal translocation of fluid). - Movement of fluid along surgically implanted tubing and vessels running to lymphadenomatous shunts. - Continuous control of applied forces and generated tissue pressures. - Standardized and reproducible limb massage. - No tissue damage.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL).



Table VI Alternative Lymphedema Medical Devices

Author	Cohort (n)	Lymphedema characteristics	Device mode of action	Treatment protocol	Results/Conclusions
Chanwimalueang et al.(83)	647	Unilateral, primary and secondary, upper and lower limb lymphedema.	Paired, cuffed and multi-belted Schnogh: manually adjustable tightening devices performing the Twisting Tourquet© Technique over multi-layered bandage systems, alternating between 15 minutes of compression and 5 minutes of decompression; pressures of 80-90 mmHg were applied in the distal limb and were slightly lessened 3-5 mmHg for each segment, generating a descending gradient distoproximally.	Daily sessions of 3,5h during 5 days; vegan diet was recommended as an adjuvant therapy.	- 55.6% of average volume reduction and 1856 mL of average edema reduction volume in LLL patients.

* Clinical lymphedema stages according to the International Society of Lymphedema (ISL).

PHARMACOLOGICAL THERAPY

No drug therapy has been shown to be effective.⁽⁹⁾ In patients with persistent or reluctant LLL, complementary pharmacological management with corticosteroids or diuretics⁽⁸⁵⁾ can be employed. Benzopyrones are not recommended due to their hepatotoxicity.⁽⁸⁶⁾ On histological evaluations, ketoprofen proved to significantly reverse inflammatory pathophysiological features, with no significant changes in limb volume or microlymphatic vascular area.⁽¹⁾ Despite its anti-filarial action, doxycycline proved to reverse and halt the progression of inflammatory lymphedema features, suggesting its potential role in the management of non-filarial lymphedema.⁽⁸⁷⁾ Intravenous pamidronate and robuvit in combination with continued conservative measures provided synergic improvements in limb volume and lymphedema-related symptoms.^(88,89) Third-generation cephalosporins have been reported in the treatment of cellulitis with lymphangitis.^(15,90)

DISCUSSION

Holistic approaches based on mechanical reduction of limb swelling have proved high levels of effectiveness, with reduction of lower limb volume, significant improvement on both pathological and imaging lymphedema features and subjective outcomes.^(39-43, 45-48, 91) This comprehensive therapies present substantial positive impact on patients QoL, with marked improvements in the physical components.^(39, 42, 47-51)

Compression therapy proved to safely manage cases of malignant lymphedema⁽⁴⁷⁾ and its efficacy increases with lymphedema severity.⁽⁴⁶⁾ It more frequently includes the combination of manual massages, bandaging, pneumatic compression, compression stocking and remedial exercises.^(39, 42, 43, 46, 47, 92) In this context, CDT stands out, which is traditionally a two-phase approach with the first intensive stage usually carried out by specialized professionals. However, this first phase did not proved to significantly impact long-term results, which are mostly dependent on patient diligence.⁽⁴⁰⁾ Since it's a high-cost and time-consuming therapy, shorter and outpatient versions have been promoted, with proven results,^(42, 43, 91) probably reducing the economic burden without compromising treatment effectiveness.⁽⁴²⁾ Nevertheless, the majority of the studies managed the more advanced lymphedema cases in hospital-based approaches.^(42,46)

Recent studies report immediate effect of MLD on skin and subcutaneous strain. Increased tissue strains were related with collagen break and release of confined fluid, whereas the temporary removal of fluid excess was responsible for lower tissue deformity and those effects were dependent on pre-MLD tissue properties.⁽⁵²⁾

PCT proved to be a highly effective mechanical drainage method and its benefits are largely proven.^(8, 32, 53, 54, 58, 59, 61, 62, 64, 65) Despite different device parameters, most of the studies present more favorable results with long-term, high pressure (80-120 mmHg) and long inflation and deflation timed (>50 seconds) PCT with sequential modes of inflation,^(8, 32, 53, 54, 58, 59, 62, 64, 65)

which demonstrated to be safe and well tolerated,^(53, 58, 65, 93) The obtained significant volume reductions were related to fluid translocation, in which interstitial channels play a predominant role, especially in the obstructive forms.^(61, 63) For that reason, volume changes caused by PCT have been shown to vary across different levels of the lower limb, according to tissue capacity to accommodate translocated fluid.^(53, 54, 58, 63) Effective tissue pressures proved to depend on pneumatic chambers applied pressures and tissues hydromechanical conditions,⁽⁵⁹⁾ which promoted some degree of dissipation.^(54, 57, 64) Tissue effects during PCT^(32, 54, 57, 59, 64) include an uneven distribution of pressures^(54, 64), a decreased permeability of the compressed tissues with consequent slowing of lymph flow⁽⁵⁹⁾ and some backward displacement of fluid once distal positive pressures are removed.⁽⁵⁴⁾

Multi-layered self-bandaging techniques have been developed⁽⁴⁶⁾ to create minimum discomfort in patient daily living and intelligent working dynamics, which is accomplished by the combination of elastic and inelastic components, enabling comfortable resting loads with effective pressure peaks during muscle contractions. Thin profiles are compatible with the use of clothing and footwear and minimum movement limitation.^(70, 71)

Recent methods have revealed significant volume reductions and imaging evidence of reduced tissue fluid, with easy and reproducible application and minimum slippage rates, as swelling goes down.^(46, 70-72)

Compression bandaging systems proved to be effective as an independent method, without compromising treatment effectiveness, with the advantage of being more accessible and less labor-intensive than CDT, particularly relevant in the elderly lymphedema population.⁽⁷²⁾

Despite the evidence of high compliance rates revealed by its prophylactic employment,⁽⁷⁶⁾ the major problem involving compression stocking is the considerable portion of patients that does not purchase the recommended therapy, due to inadequate use or non-application. The difficulty with its application, the costs associated and the feeling of disbelief in stocking effectiveness contribute to its incipient use. Poor compliance was associated with disease progress and increased number of hospitalizations, in a paradigm of proven high duration of illness.⁽⁷⁴⁾ Properly fitted compression stocking have been proved to maintain lymphedema reductions and improve patients satisfaction.^(41, 49, 75, 91) Considering the importance of patient tolerance and compliance, some authors defend the prescription of lower pressures in the initial treatment phase and that garment selection process should take into account the patient's preference.⁽⁷⁴⁾

Structured exercise protocols are associated with significant reductions of chronic LLL and may be a potential first-line therapeutic approach to primary care, presenting a good cost-benefit ratio and high levels of compliance. The methods

applied take into account the dependent leg position and exercises are performed in standing or lying position, frequently including bicycling activities. Studies are designed to maximize the ankle motion together with the calf and plantar muscle pumps and some authors defend the inclusion of strengthening and high-load exercises.^(50, 77, 78)

Some alternative medical apparatus proved to be safe and effective, even when applied on an outpatient-basis.^(45, 81, 91)

Application of bioresonance microcurrents has proven beneficial effects in association with different complementary mechanisms.^(80, 81) Usually, the employment of this devices is associated with high compliance rates and promotes the standardization of some therapeutic procedures.⁽⁸⁰⁻⁸²⁾

Recently employed pharmacological therapies include anti-inflammatory, anti-oxidant and neural mediation action.^(1, 88, 89)

Anti-inflammatory therapies focus on the skin as the primary target organ of the lesion, evidencing the histologic changes.⁽¹⁾

Some drugs have shown synergistic effects when associated with compression therapy^(88, 89) and pharmacological therapy has even proved to reverse lymphedema severity.⁽⁸⁷⁾

CONCLUSION

The non-surgical approach of LLL commits both the patient and health care providers to comply with life-long measures.

Therapeutic effects are mainly achieved by the employment of compression in the affected areas, combining external compression modalities with internal forces induced by muscular contraction.

Drainage techniques, such as manual drainage and pneumatic compression, are associated with tissue fluid translocation towards the limb areas with the lowest hydraulic resistance. Despite being associated with increased circumference in those areas, they allow marked limb volume reductions specially in the initial stages of the treatment. Moreover, decreased fluid stagnation prevents secondary tissue fibrosis and progression to more severe forms.

Contention measures, including bandaging and compression hosiery, are designed to preserve the volume reductions achieved by drainage techniques, although they may induce further limb volume reductions. Poor compliance lies in difficulties with their application and induced discomfort, associated with prolonged required time of use. Continuous adjustments are necessary, taking into account edema evolution.

The greatest advantage of physical exercise lies in the application of physiological mechanisms, which promote substantial positive effects on functional capacity and psychological state. For this reason, patient education and motivation should be considered central aspects of non-surgical therapy. Patients involvement in treatment decisions and personalized



professional care allows better transmission of the techniques and establishes more concrete goals, ultimately promoting a greater belief in therapy effectiveness.

Some systemic approaches, such as anti-inflammatory therapy, have been under recent investigation, raising hope for meaningful advances in the near future.

Limitations of the conservative treatment highlight the importance of preventive measures. Anti-filarial therapies recently proved to reverse lymphatic pathology, suggesting that they may play a role in lymphedema treatment.

Research into the molecular pathogenesis will probably allow the development of effective target therapies, that might become a reality in the future.

Health professionals lack proper education about the correct diagnostic and therapeutic procedures, thus the future of the LLL approach must be filled by increased global awareness, improved education and more effective therapeutic interventions.

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