

Lipedema

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1. Introduction

Lipedema is a sparsely recognized clinical entity almost entirely affecting the female population. It poses a significant importance as being one of the most common disorder to be mistaken with lymphedema and obesity [1,2,3,4].

2. Definition

Lipedema is a disproportional, bilateral, symmetrical fatty swelling of the legs whereas arms are also commonly involved [1,2,3,4,5]. Generally, first symptoms appear around puberty [2,3,4]. Almost solely women are affected and males usually develop lipedema on the basis of hormonal disturbance [6]. The general incidence of lipedema among women is reported to be up to 11% [2]. Lipedema is presumably due to endocrinological and genetic background [2,7,8]. Two prominent hallmarks are the frequent spontaneous or minor trauma-induced bruising and spontaneous or palpation-induced pain [1,2,3,4]. Lipedema, especially in untreated cases, is commonly associated with lymphatic and/or venous insufficiency [2,3,4]. Lipedema is commonly combined with obesity making differential diagnosis considerably difficult [2,3,4]

3. Clinical diagnosis

In most cases the diagnosis of lipedem is simply set using patient history and clinical examination [2,3,4]. There is no absolutely unambiguous pathognomonic diagnostic test for lipedema.

3.1 Classification

In stage I, the skin looks flat, but the subcutis is thicker and on palpation feels like 'styrofoam balls in a plastic bag'. In stage II walnut- to apple-sized indurations appear and the overlying skin has an irregular surface ('mattress phenomenon'). Stage III shows large, sometimes lobular fat deposits. The location-based classification concurs with the area of the fat deposits: mainly buttocks (type I), buttocks to knees (type II), buttocks to ankles (type III), mainly arms (type IV) and mainly lower legs (type V) [9].

3.2 Differential diagnosis

The differential diagnosis of lipedema embraces obesity, various forms of lipohypertrophy and phleb- or lymphedema.

3.3 Instrumental diagnosis

These tests comprise waist-to-height ratio as an anthropometric measure [10], Streeten test for capillary permeability [11] and vacuum suction method with Parrot's angiostrometer for capillary fragility assessments [2,3,4,12], evaluation of aortic stiffness [13], subjective pain perception [14,15,16]. Accurate techniques as high resolution ultrasonography [17,18], computer tomography [19], magnetic resonance imaging [20,21], lymphoscintigraphy [22,23], fluorescent microlymphography [24] are also useful in diagnosis or making differential diagnosis.

4. Clinical management

4.1 Evidences in lipedema care

4.1.1 The conservative approach in the intensive therapeutical phase

corresponds to complex decongestive physiotherapy (CDP) consisting of manual lymph drainage (MLD), intermittent pneumatic compression (IPC) as a possible supplementary treatment, physical exercise, multilayered and multicomponent compression bandaging and meticulous skin care [2]. The first observational study disclosed a maximally achieved reduction by CDP as nearly 10% of the original leg girth [25]. In an other clinical setting MLD-based CDP was compared with MLD+IPC along with compression. Each treatment modality turned out significant limb volume reductions, however no significant difference was proven between the two regimens in that pilot study [26]. Further controlled trials showed that MLD+IPC-based CDP drastically decreased capillary fragility and pain perception of lipedema patients [12].

Gentle forms of liposuction give reliable benefit to lipedema patients without proven relevant damage of lymphatics [27].

4.1.2 Maintenance phase

includes skin care, daily wear of support garments (stockings or hosiery). Nocturnal bandaging might be applied. [28,29,30,31,32].

4.2 General description of physiotherapy and compression material

4.2.1 Manual lymph drainage

Although there is a relatively strong empirical body advocating the benefits of MLD, research data barely support its use in lymphatic insufficiency [33,34,35,36,37] or in lipedema. Beyond its well-known benefits, MLD is able to improve blood microcirculation blood flow, has peripheral analgesic, central sedative, analgesic, vagotonic reaction [38,39,40,41] and improves muscular recovery after physical exercise [42].

4.2.2 Steps of manual lymph drainage after Dr. Vodder in various forms of leg lipedema [33]

Central treatment: All proximal lymphatic drainage pathways must be cleared before any attempt to move lymph into them from a more distal area.

Supine position:

Contact with the neck region

Deep abdominal treatment

Treatment of axillar region and inguino-axillar anastomoses of both sides

Decongestion of both lower edematous body quadrants to the direction of axillary lymph nodes of identical sides

Treatment of lower body quadrants (emptying the quadrant)

Prone position:

Treatment of inguino-axillar anastomoses of both sides

Decongestion of gluteal region to the direction of axillary lymph nodes of identical sides

Treatment of lower body quadrants (emptying the healthy quadrant)

Leg treatment

Supine position:

Stimulation of inguinal lymph nodes

Decongestion of the lateral side of the thigh

Drainage from the lateral to the medial side of the thigh

Drainage from the distal to the proximal part of the thigh

Stimulation of the knee region

Drainage from the distal to the proximal part of the calf

Drainage from the distal to the proximal part of the foot

Prone position:

It is consistent with the previous steps in supine position, however the stimulation and decongestion of retromalleolar region is also mandatory.

Leg treatment steps should be repeated so as to treat all regions several time

4.3 Intermittent pneumatic compression

IPC is assumed to reduce oedema by decreasing capillary filtration, rather than by accelerating lymph flow. IPC alone is particularly effective in nonobstructive edemas like lipedema. Clinical trials prefer the utilization of multi-chambered pumps to single-chambered ones [43,44], however pressures should be adjusted according to individual response. In general, pressures of 30-60 mmHg are mostly applied, however higher pressures also improve limb edema and lower pressures (20-30 Hgmm) are advised in palliative care and a duration of 30 minutes to two hours daily is recommended [45,46]. IPC is outstandingly efficacious in the edema treatment of immobile patient [47]. It is able to squeeze the water content of a lymphedematous extremity without improving the lymphatic drainage to an adequate amount leading to an increase of the oncotic tissue pressure necessitating a continuation of compression therapy [48]. IPC may exacerbate or cause congestion at the noncompressed root of a treated limb and also in the adjacent, genital region [49]. Recent examinations showed remarkable induction of lymph return in lymphedema [50].

4.4 Compression

Compression therapy is recognized as one of the most effective treatment modalities in the management of venous and lymphatic disease. Until recently, evidence of efficacy was based mostly on empirical study. Experimental data on the effect of conventional compression therapy on lymphedema are sparse. Effects of compression include shape and volume

restoration and remodelling, improvement of skin changes, elimination of lymphorrhoea, subcutaneous tissue softening. There is a strong recommendation for the management of acute deep vein thrombosis, chronic venous insufficiency and lymphoedema with compression therapy [51,52,53]. Patients with lower limb lymphoedema with reduced ankle-brachial pressure index (ABPI) of 0.5-0.8 should not receive sustained compression exceeding 25 mmHg. Patients with ABPI <0.5 can mostly receive only intermittent compression. [54] Compression therapy comprises the use of compression bandages or stockings.

4.4.1 Multilayer compression

It is a treatment of choice when we use bandages to achieve appropriate compression. The principles are seen as follows:

1. Skin care prevents dryness and consequent microinjuries of the epidermis
2. Finger or toe bandaging may prevent or reduce toe swelling
3. Tubular cotton bandage provides a protective layer between the skin and other bandages
4. Subbandage padding (soft synthetic wool, foam roll or sheet) protects the skin and subcutaneous tissues, normalizes shape, protects bony prominences and equalizes the distribution of pressure produced by outermost bandage layers.
5. Dense foam is applied locally to soften hard areas of tissue thickening and fibrosis or areas particularly vulnerable to oedema (ankles).
6. Inelastic bandages (non-adhesive, adhesive or cohesive bandages) should be applied at nearly full extension and 50% overlap. Elastic bandages should be applied at 50% extension and overlap. Several pieces of bandages are used to achieve desired pressure.
7. Adhesive tapes or cohesive bandages fix compression bandages and stabilize the whole compression system

To achieve optimal volume reduction, high initial interface pressures are necessary to compensate pressure decrease. The pressure drop is already significant after 2 hours and mainly caused by volume reduction explaining the need for a more frequent bandage change in the beginning of lymphedema therapy compared to the current practice where change of bandage system is recommended once a day in the initial phase [55].

In general, inelastic compression depending on the strength of tensile pressure and stiffness can be worn overnight without major influence on microcirculation, hence subbandage pressure does not significantly interfere with capillary function in supine position.

Unlike inelastic compression, the nocturnal wear of elastic bandages is normally not recommended due to the relatively high interface pressure in supine position and in case of diminished arterial influx severe occlusion can occur.

When compression with bandages is applied, exerted pressure can be calculated using Laplace's law: $P = T \times N / C \times W$ (P = sub-bandage pressure (mmHg), T = bandage tension (kilograms force), N = number of layers, C = limb circumference (cm), W = bandage width (cm).

Pressure, Layers, Components, and Elastic properties (P-LA-C-E) are the main factors that have to be taken into consideration when a compression bandage is applied.

Pressure measured *in vivo* in the medial gaiter area in the supine position for training purposes may be classified into the following categories:

mild (<20 mmHg), moderate (20–40 mmHg), strong (40–60 mmHg), or very strong (>60 mmHg).

Layers: A double-layer bandage is characterized by an overlap of at least 50%. Components of a bandage consist of same or different materials that may have different functions (padding, protection, retention). **Elasticity:** The elastic properties of a single bandage may be inelastic (rigid bandages or short-stretch bandages) or elastic (long-stretch bandages). Inelastic bandage extensibility is under 100% of the original length. Several layers of material (either identical or different materials) have the tendency to make the bandage system stiffer. In the lymphology practice we encourage the application of inelastic bandages because they exert high working pressure in active physical exercises and depending on tension forces during pulling of bandages evoke relatively low resting pressure at lying position.

Multilayer bandage systems may behave as inelastic systems even though the individual layers act as elastic materials due to the friction generated between bandage layers. Therefore, in case of multilayer bandage systems and kits, the terms “high or low stiffness” should be used to describe the behavior of the final bandage. Stiffness is defined as the increase of interface pressure measured in the gaiter area when standing up from the supine position. A raise in the pressure of more than 10 mmHg measured in the gaiter area is characteristic of a stiff bandage system [53].

4.4.2 Use of elastic bandages

In some situations (ineffective calf muscle pump, phlebolympheoedema, large volume loss is predicted, extremely large adipose tissue deposition and low potential of muscle pump), the inelastic bandages may be replaced with elastic ones. The stiffness produced by multiple layers produces high working pressure. However, the resting pressure is usually higher than with inelastic systems at the same strength of application of both bandage systems.

4.5 Medical compression stockings

Compression garment utilization comprises the the long-term management of lipedema in maintenance phase. Limbs with relatively normal shape require round-knitted stockings while flat-knitted stockings better fit to limbs with unusual shape or remarkable distortion than round-knitted ones. Appropriate and well-fitting medical compression stockings in lipedema are mostly custom-made because lipedematous legs usually do not belong to average sizes.

In general, compression stockings have a lower stiffness index than inelastic bandages, especially when these bandages are worn in a multilayered fashion. MCSs drop their pressure to a much less degree compared to compression bandages [56,57,58].

4.6 Exercise

Exercise/movement should be tailored to the patient ability and disease status. Compression should be worn during exercise whenever it is possible. Walking, swimming, cycling and low impact aerobics are recommended.

5. Prognosis

Lipedema is a progressive disorder but in few cases may remain self-limited. Early diagnosis and treatment are cornerstones for this disorder otherwise gradual enlargement of

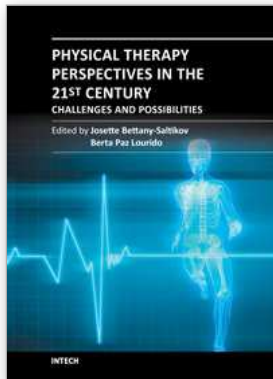
massive fatty tissue causes severely compromised mobility, debilitating condition and further co-morbidities like arthrosis and lymphatic insufficiency. Interlobar areas may become susceptible for infections that may further progress to cellulitis or septicaemia. Lipedema has remarkable psychological impact ranging from mild upset to severe anxiety, depression or even anorexia [2,3,4].

6. References

- [1] Allen, EV, EA Hines. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema. *Mayo Clin. Proc* 1940;15:184-7.
- [2] Földi E, Földi M. [Das Lipödem] in Földi M, Kubik S eds, *Lehrbuch der Lymphologie*, 5nd edn, Chapt 9. München-Jena:Gustav Fischer, 2002:449-58.
- [3] Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM. Lipoedema: from clinical presentation to therapy. A review of the literature. *Br J Dermatol* 2009;161:980-6.
- [4] Todd M. Lipoedema: presentation and management. *Br J Community Nurs* 2010;15:S10-6.
- [5] Meier-Vollrath I, Schneider W, Schmeller W: Lipödem: [Verbesserte Lebensqualität durch Therapiekombination]. *Dtsch Ärzteblatt* 2005;102:1061-7.
- [6] Chen S, Hsu SD, Chen TM, Wang HJ. Painful fat syndrome in a male patient. *Br J Plast Surg* 2004; 57:282-6.
- [7] Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S, et al. Lipoedema: an inherited condition. *Am J Med Genet Part A*:152A:970-6.
- [8] Szolnoky G, Kemeny L. Lipoedema: from clinical presentation to therapy: Further aspects. *Br J Dermatol* 2010;162:889.
- [9] Meier-Vollrath I, Schneider W, Schmeller W: [Das Lipödem: neue Möglichkeiten der Therapie]. *Schweiz Med Forum* 2007;7:150-5.
- [10] Herpertz U. [Adipositas-Diagnostik in der Lymphologie]. *LymphForsch* 2009;13:90-3
- [11] Streeten DH. Idiopathic edema. Pathogenesis, clinical features, and treatment. *Endocrinol Metab Clin North Am* 1995;24:531-47.
- [12] Szolnoky G, Nagy N, Kovács RK, Dósa-Rácz E, Szabó A, Bársony K, et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. *Lymphology* 2008;41:161-6.
- [13] Nemes A, Gavallér H, Csajbók É, Forster T, Csanády M. Obesity is associated with aortic enlargement and increased stiffness: an echocardiographic study. *Int J Cardiovasc Imaging* 2008;24:165-71.
- [14] Schmeller W, Meier-Vollrath I. [Schmerzen beim Lipödem: Versuch einer Annäherung]. *LymphForsch* 2008;12:7-11.
- [15] Hamner, JB, Fleming MD. Lymphedema therapy reduces the volume of edema and pain in patients with breast cancer. *Ann. Surg. Oncol.* 2007;14:1904-8.
- [16] Wong DL, Baker CM: Smiling faces as anchor for pain intensity scales. *Pain* 2001;89:295-300.
- [17] Marshall M, Schwahn-Schreiber C. [Lymph-, Lip- und Phlebödem. Differenzialdiagnostische Abklärung mittels hochauflösender Duplexsonographie]. *Gefäßchirurgie* 2008;13:204-12.
- [18] Naouri M, Samimi M, Atlan M, Perrodeau E, Vallin C, Zakine G et al. High resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema. *Br J Dermatol* 2010 Apr 16 [Epub ahead of print].
- [19] Vaughan BF. CT of swollen legs. *Clin Radiol* 1990;41:24-30.
- [20] Dimakakos PB, Stefanopoulos T, Antoniadis P, . MRI and ultrasonographic findings in the investigation of lymphedema and lipedema. *Int Surg* 1997;82:411-6.

- [21] Lohrmann C, Foeldi E, Langer M. MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. *Microvasc Res* 2009;77:335-9.
- [22] Brauer WJ. [Altersbezogene Funktionslymphszintigraphie beim Lipödem und Lipolymphödem]. *LymphForsch* 2000;4: 74-7.
- [23] Harwood CA, Bull RH, Evans J, Mortimer PS. Lymphatic and venous function in lipedema. *Br J Dermatol*.1996;134:1-6.
- [24] Amann-Vesti BR, Franzeck UK, Bollinger A. Microlymphatic aneurysms in patients with lipedema. *Lymphology* 2000;134:170-5.
- [25] Deri G, Weissleder H: [Vergleichende prä- und posttherapeutische Volumenmessungen in Beinsegmenten beim Lipödem]. *Lymph Forsch* 1997; 1: 35-7.
- [26] Szolnoky G, Borsos B, Bársony K, Balogh M, Kemény L. Complete decongestive physiotherapy of lipedema with or without pneumatic compression: a pilot study. *Lymphology* 2008;41:50-2.
- [27] Schmeller W, Meier-Vollrath I. Tumescence liposuction: a new and successful therapy for lipedema. *J Cutan Med Surg* 2006;10:7-10.
- [28] Wozniwski M, Jasinski R, Pilch U, Dabrowska G: Complex physical therapy for lymphoedema of the limbs. *Physiotherapy* 2001;87:252-6.
- [29] Wozniwski M, Pilch U, Jezierski C: Physiotherapy for patients with lower extremity lymphoedema. *Phlebology* 1995: suppl 1:1051-3.
- [30] Lymphoedema Framework. Best Practice for the Management of Lymphoedema. International consensus. London: MEP Ltd, 2006:3-52.
- [31] Ko TS, Lerner R, Klose G, Cosimi AB: Effective treatment of lymphedema of the extremities *Arch Surg* 1998;133: 452-8.
- [32] Vignes S: Physical therapy in limb lymphedema La kinésithérapie dans le traitement des lymphoedèmes des membres). *Ann Dermatol Venereol* 2005;132:185-7.
- [33] Strössenreuther RHK. [Hinweise zur Durchführung der ML/KPE bei primären und sekundären Lymphödemen sowie weiteren ausgewählten Krankheitsbildern] in Földi M, Kubik S eds, *Lehrbuch der Lymphologie*, 5nd edn, Chapt 19. München-Jena:Gustav Fischer, 2002:621-658.
- [34] Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev* 2004; 4: CD003141.
- [35] McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, Hanson J. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat* 2004;86: 95-106.
- [36] Johansson K, Albertsson M, Ingvar C, Ekdahl C. Effects of compression bandaging with or without manual lymph drainage treatment in patients with postoperative arm lymphedema. *Lymphology* 1999;32:103-10.
- [37] Vignes S, Coupé M, Baulieu F, Vaillant L;Groupe Recommandations de la Société Française de Lymphologie. Limb lymphedema: Diagnosis, Exploration, complications. *J Mal Vasc* 2009;34:314-22.
- [38] Hutzschenreuter P, Brümmer H, Ebberfeld K. Experimental and clinical studies of the mechanism of effect of manual lymph drainage therapy. *Z Lymphol* 1989;13:62-64.
- [39] Trettin H. Manual lymph drainage in migraine treatment - a pathophysiologic explanatory model. *Z Lymphol* 1989;13:48-53.
- [40] Hutzschenreuter P, Ehlers R. Effect of manual lymph drainage on the autonomic nervous system. *Z Lymphol* 1986;10:58-60.
- [41] Kurz W, Wittlinger G, Litmanovitch YI, Romanoff H, Pfeifer Y, Tal E, et al. Effect of manual lymph drainage massage on urinary excretion of neurohormones and minerals in chronic lymphedema. *Angiology* 1978;29:764-72.

- [42] Schillinger A, Koenig D, Haefele C, Vogt S, Heinrich L, Aust A, et al. Effect of manual lymph drainage on the course of serum levels of muscle enzymes after treadmill exercise. *Am J Phys Med Rehabil* 2006;85:516-520
- [43] International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. *Lymphology* 2009;42:51-60.
- [44] Bergan JJ, Sparks S, Angle N. A comparison of compression pumps in the treatment of lymphedema. *J Vasc Surg* 1998;32:455-62.
- [45] Partsch H, Mostbeck A, Leitner G. Experimentelle untersuchungen zur Wirkung einer Druckwellenmassage (Lymphapress) beim Lymphödem. *Phlebol. U Proktol* 1980;9:124-8.
- [46] Szuba A, Achalu R, Rockson SG. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomised, prospective study of a role of adjunctive pneumatic compression. *Cancer* 2002;95:2260-7.
- [47] Partsch H: Intermittent pneumatic compression in immobile patients. *Int Wound J* 2008;5:389-97.
- [48] Miranda F Jr, Perez MC, Castiglioni ML, Juliano Y, Amorim JE, Nakano LC, et al. Effect of sequential intermittent pneumatic compression. *Lymphology* 2001;34:135-41.
- [49] Boris M, Weindorf S, Lasinski BB. The risk of genital edema after external pump compression for lower limb lymphedema *Lymphology* 1998;31:15-20.
- [50] Olszewski WL, Cwikla J, Zaleska M, Domaszewska-Szostek A, Gradalski T, Szopinska S. Pathways of lymph and tissue fluid flow during intermittent pneumatic massage of lower limbs with obstructive lymphedema. *Lymphology*. 2011 Jun;44(2):54-64.
- [51] Badger CM, Peacock IL, Mortimer P. A randomised controlled parallel group clinical trial comparing multilayer bandaging followed by hosiery *versus* hosiery alone in the treatment of patients with lymphoedema of the limb. *Cancer* 2000;88:2832-7.
- [52] Badger C, Seers K, Preston N, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.
- [53] Partsch H, Clark M, Mosti G, Steinlechner E, Schuren J, RN, Abel M, et al. Classification of Compression Bandages: Practical Aspects. *Dermatol Surg* 2008;34:600-9.
- [54] Marston W, Vowden K. Compression therapy: a guide to safe practice. In: European Wound Management Association (EWMA). Position Document: Understanding compression therapy. London: MEP Ltd, 2003: 11-7.
- [55] Damstra RJ, Brouwer E, Partsch H. Controlled, comparative study of relation between volume changes and interface pressure under short-stretch bandages in leg lymphedema patients. 2008;34:773-9.
- [56] Partsch H, Partsch B, Braun W. Interface pressure and stiffness of ready made compression stockings: Comparison of in vivo and in vitro measurements. *J Vasc Surg* 2006;44:809-14.
- [57] Vignes S. Elastic garment in management of lymphedema (Interet de la compression élastique dans le traitement des lymphoedèmes). *Ann Dermatol Venereol* 2005;132:290-1.
- [58] Larsen AM, Futtrup I. Watch the pressure - it drops! *EWMA Journal* 2004;4:8-12.



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