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S1 Guideline on Lipedema

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ICD 10 R60.9 Edema, unspecified

Introduction

In clinical practice, questions about the diagnostics and treatment of lipedema arise regularly. Often, symptoms are mixed with those of concurrent diseases (e.g., lipedema and obesity, lipedema and lymphedema), which can be difficult to distinguish in differential diagnostics.

For the diagnostics and treatment of lymphedema, please note the guideline issued by the Society of German-Speaking Lymphologists (Gesellschaft Deutschsprachiger Lymphologen – GDL) (GDL 2009). For the diagnostics and treatment of obesity, please note the guideline issued by the German Obesity Society (Deutsche Adipositas-Gesellschaft) (DAG 2014).

This guideline focuses on the diagnostics and treatment of lipedema.

1. **Definition**

Lipedema is a chronic progressive disease that occurs almost exclusively in women and is characterized by a fat distribution disorder with distinct disproportion between the trunk and limbs. This disproportion arises due to a localized, symmetric excess of subcutaneous fat tissue in the lower and/or upper limbs (Herpertz 1997). In addition, patients exhibit edema worsened by orthostasis as well as easy bruising following the slightest trauma (Allen 1940, Wienert 1991, Herpertz 2014). Further characteristics of lipedema include increased pressure-induced pain and in most cases spontaneous pain.

2. **Synonyms**

Often, the following terms are used synonymously. Whether they actually describe the same clinical picture is the subject of debate: lipomatosis dolorosa, lipohypertrophy dolorosa, adiposis dolorosa, lipalgia, adiposalgia, painful column leg, painful lipedema syndrome, lipohyperplasia dolorosa

3. **Prevalence**

The disease occurs almost exclusively in women. Lipedema typically initially manifests during times of hormonal change, such as in puberty, pregnancy or menopause.

In men, changes similar to lipedema have only been described in case of treatment with hormonal effect, severe hormone disorders (e.g., hypogonadism), or hepatic cirrhosis (Weissleder 2011, Wold 1951, Child 2010, Chen 2004).

In terms of epidemiology, no confirmed data from large studies are available. Depending on the patient population examined and the diagnostic criteria applied, most outpatient studies showed a prevalence of 7-9.7% (Földi 2007, Marshall 2011, Miller 2008); however, some report much lower figures (0.1%) (Herpertz 2014). Studies conducted among female inpatients of lymphological specialty clinics showed a prevalence between 8% and 18% (Herpertz 1997, Meier-Vollrath 2005, Lulay 2010).

Due to widespread diagnostic uncertainty, a high number of undiagnosed cases is likely. On the other hand, some patients who do not meet the criteria are wrongly diagnosed with lipedema.

4. **Etiopathogenesis**

The etiology is still unknown. The exact pathomechanisms and the special role of hormones and their receptors are also still unclear (Szel 2014). In up to 60% of cases, a genetic component with a family history of lipedema is described (Greer 1974, Wold 1949, Harwood 1996, Fife 2010). In six families with lipedema, for instance, an autosomal dominant inheritance pattern with incomplete penetrance was shown over three generations (Child 2010).

The localized fatty tissue excess is the result of adipocyte hypertrophy and hyperplasia (Kaiserling 2005). In addition, connective tissue changes can be observed (Brenner 2009). Patients also exhibit capillary permeability disorder (Weissleder 1997), which causes more fluid to enter the interstitial space from the vascular system. The increased capillary fragility causes the noticeable tendency to bruise easily (Szolnoky 2008b).

Due to the higher fluid supply, the initially intact lymphatic vessels respond with increased lymph transport (Brauer 2005). It is hypothesised that long-term strain on the lymphatic vessels causes degenerative changes in the vessel walls with resulting reduction of transport capacities (high-volume insufficiency). Edema develops when the lymph collecting largely in dependent areas cannot be adequately drained. In the course of several years, subcutaneous fat and edema can increase.

In orthostasis, lipedema patients also exhibit delayed and reduced veno-arterial reflex (VAR). The VAR impairment favors orthostatic edema. This impairment can be significantly alleviated with compression bandaging (Stößenreuther 2001).

In the further course of disease, some patients exhibit lipedema with secondary lymphedema (so-called lipo-lymphedema), not always with a positive Stemmer's sign. In the advanced stage, secondary changes such as sclerosis and papillomatosis are found due to fibroblast proliferation in the dermis. As a result of increasing fibrosis of the subcutaneous fat tissue, mechanical insufficiency develops (Földi 2005, Brauer 2002, Brauer 2005).

The histological changes found in lipedema are not pathognomonic. In addition to an increase in adipocytes, some of which are hypertrophic, the interstitial space contains an elevated number of capillary blood vessels; perivascularly, one finds macrophages, fibroblasts, mast cells and in some cases adipose tissue necrosis. In the late stages of the disease, the fibrotic component increases (Kaiserling 2005). Immunohistological studies have shown degenerative and regenerative changes of the adipose tissue, characterized by crown-like structures of necrotic adipocytes surrounded by infiltrating CD68+ macrophages and proliferations of fat-associated stem/progenitor cells and connective tissue cells (Ki67- and CD34-positive). These findings support the hypothesis of increased adipogenesis in the lipedema tissue (Suga 2009).

5. Clinical course

The changes associated with lipedema always arise symmetrically in the legs and/or arms (Herpertz 2004, Cornely 2002). The excess fat can homogeneously distribute over the thighs and/or calves (column-like legs) or arms and/or forearms (**Table 1**). A typical sign is the change in caliber to the adjacent healthy region ("bracelet effect", "band-like appearance").

Table 1: Categorization of lymphedema by localization (modified acc. to Herpertz 2014).

Legs	Arms
Thigh type	Upper arm type
Whole leg type	Whole arm type
Calf type	Lower arm type

Many patients also exhibit a mixed type. Solitary lipedema of the arms without involvement of the legs is extremely rare.

In the later course, many patients also exhibit rolls of fat that are primarily located at the insides of the thighs, knees, and more rarely the ankle joint. Rubbing effects cause tissue trauma (chronic irritant contact dermatitis), while occlusive effects of the skin folds cause macerations and consecutively infections. The rolls at the insides of thighs also interfere with the gait, causing axial malalignment of the legs and orthopedic complications (largely valgus gonarthrosis) (Stutz 2009).

The quality of life of affected patients is often severely reduced. One the one hand, this is the result of the increased volume and the disproportion between trunk and limbs, and on the other, of a tightness sensation with pain on touch and pressure, which is particularly pronounced in warm weather, after extended standing or sitting, and in the evenings. Some patients also experience considerable spontaneous pain. The pain is largely described as dull, pressing, and heavy (Schmeller 2008).

The disease is chronic progressive. Three morphological stages of lipedema can be differentiated (Fife 2010, Meier-Vollrath 2004) (**Table 2**). The disease progresses individually and unpredictably. The stage definition is not necessarily linked with the severity of clinical symptoms (pain).

Table 2: Classification of lipedema based on morphology. The changes can occur in arms or legs.

Stage	Characteristics
1	Smooth skin surface with evenly enlarged, homogeneous-looking hypodermis
2	Uneven, largely wavy skin surface, nodular structures in the enlarged hypodermis
3	Considerably enlarged circumference with bulge and cuff development

Progression to lipedema with secondary lymphedema can occur in any stage and is to some extent dependent on comorbidities (such as obesity and inactivity) (Herbst 2012). Concomitant obesity can aggravate the course and symptoms of lipedema (Marshall 2008 a).

6. **Diagnostics**

The goal is to diagnose lipedema early through history taking, inspection and palpation and on the basis of the typical characteristics (Forner-Cordero 2012, **Table 3**). Other causes of edema should be ruled out. Additional diagnostics may be necessary for this purpose.

To facilitate follow-up, it is recommended to document additional parameters such as weight, body mass index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) as well as limb circumference and volume measurements and the daily activity index. Particularly in cases that pose a challenge in terms of differential diagnostics (obesity versus lipedema), these follow-up parameters can be helpful in the diagnosis of lipedema if the limb volume fails to drop despite reduction of overall weight and trunk fat (Dutch Society of Dermatology 2014).

Table 3: Overview of clinical criteria for the diagnosis of lipedema

Lipedema:

- Onset in puberty, pregnancy, or menopause
- Disproportionate increase in adipose tissue (limbs vs. trunk)
- Cuff or bulge development around joints
- Hands and feet not affected
- Heaviness and tension in the affected limbs
- Pain upon palpation or spontaneous pain – worsening over the course of the day
- Edema – worsening over the course of the day
- Easy bruising
- Negative Stemmer’s sign

Morphological techniques can be used for the quantitative assessment of the subcutaneous fatty tissue and follow-up. However, findings are not very specific (especially when differentiating the condition from symmetric lipohypertrophy). With high-resolution sonography, for instance, homogeneous enlargement of the hypodermis with evenly increased echogenicity and hyperechoic septa in the absence of anechoic fissures has been described (Marshall 1996). A nonspecific thickening of the hypodermis can also be shown with computed tomography (Vaughan 1990, Werner 1993) and magnetic resonance tomography (Duewell 1992, Dimakakos 1997), but it cannot be used to confirm the diagnosis.

Morphological examinations of the lymphatic system by means of indirect lymphography showed typical but not pathognomonic changes in the form of feathery or flame-shaped deposits of contrast agent (Partsch 1988, Tiedjen 1992, Weissleder 1997).

Fluorescence microlymphography has demonstrated microaneurysms (Amann-Vesti 2001 and 2002). Fluorescence microlymphangiography can be performed with fluorescence-marked dextran or indocyanine green (Amann-Vesti 2001, Schingale 2013).

Functional testing of the lymphatic system has been performed using standardized (dynamic and static) functional lymphoscintigraphy (Bilancini 1995, Brauer 2000 and 2002, Harwood 1996, Weissleder 1995, Boursier 2004). In some patients, no noticeable changes were found (Bräutigam 1998), while others exhibited increased lymph transport in the early stages of disease (high volume insufficiency) and extended transport time with pathological lymph node uptake values in the later stages (Brauer 2005).

The listed functional testing and imaging is not required in the clinical routine diagnostics of lipedema. However, it may be useful for differential diagnostics and to address scientific questions as well as for follow-up examinations.

7. Differential diagnostics

Important differential diagnostics are shown in two tables (**Table 4 and Table 5**).

Table 4: Typical clinical signs used to differentiate lipedema, lipohypertrophy, obesity, and lymphedema

	Lipedema	**Lipohypertrophy**	**Obesity**	**Lymphedema**
Increased fat tissue	+++	+++	+++	(+)
Disproportion	+++	+++	(+)	+
Edema *	+++	Ø	(+)	+++
Pain on pressure	+++	Ø	Ø	Ø
Easy bruising	+++	(+)	Ø	Ø
Symbols: + to +++ present; (+) possible; Ø not present *The severity of edema is variable and depends on the amount of prior therapy and the stage of disease.				

Table 5: Additional differential diagnostics including treatment options (modified from Miller 2014). Intermittent pneumatic compression (IPC) can be used to supplement MLD, never to replace it.

Diagnosis	**Symptoms**	**Treatment options**
Lipedema	Symmetric, predominantly affecting the limbs, disproportionate Pain Easy bruising	Compression MLD (manual lymph drainage) IPC (intermittent pneumatic compression)

	Local edema, orthostatically aggravated	Liposuction
Lymphedema	Edema, typically including feet/hands Stage-dependent induration/fibrosis Typically positive Stemmer's sign Papillomatosis cutis, lymph cysts, lymph fistulas	MLD Compression Exercise with compression IPC Skin care Breathing exercises
Lipedema with secondary lymphedema	Symmetric, predominantly affecting the limbs, disproportionate Pain Easy bruising Local edema, orthostatically aggravated Edema of hands or feet Positive Stemmer's sign Secondary changes of the lymphedema (see above)	MLD Compression Exercise with compression IPC Skin Care Breathing exercises Liposuction if necessary
Lipedema with concomitant obesity	Combined symptoms of lipedema and obesity, see above and below	Weight reduction Compression MLD IPC Liposuction only after weight reduction
Phlebedema	Edema of the legs/arms Skin signs of CVI: stasis dermatitis, hyperpigmentation, dermatosclerosis, phlebectasia, corona phlebectasia, atrophie blanche, ulcerations	Compression IPC Treatment of the varicosity
Lipohypertrophy	Localized lipohypertrophy	Liposuction
Obesity	Generalized lipohypertrophy	Weight reduction
Obesity with secondary edema (obesity-related edema)	Generalized lipohypertrophy with secondary edema	Weight reduction Compression
Obesity with fibromyalgia	Generalized lipohypertrophy and pain	Weight reduction Treatment of fibromyalgia
Lipomatosis	Benign symmetric lipomatosis, particularly type III (pelvic region)	Liposuction
Myxedema	Doughy edema	Treatment of thyroid dysfunction

8. **Treatment**

Treatment pursues two goals:

a) Eliminate or ameliorate findings and symptoms (particularly pain, edema, and disproportion, **Table 6**).

b) Prevent complications. When findings progress, particularly with increasing leg volume, the risk of dermatological complications (e.g., maceration, infection), lymphatic complications (e.g., erysipela, lymphedema), and orthopedic complications (gait alterations, axial malalignment) rises.
No causal treatment is known. Symptomatic treatment (8.1-8.4) is individualized and administered based on the respective stage.

Table 6: Overview of currently available treatment options with their respective treatment goals (modified according to Reich-Schupke 2013).

Treatment goal	**Treatment measures**
Edema reduction	Compression MLD (manual lymph drainage) IPC (intermittent pneumatic compression) Exercise Liposuction
Pain alleviation	Compression MLD IPC Liposuction
Reduction of easy bruising	MLD IPC Liposuction
Reduction of pathologically increased subcutaneous adipose tissue	Liposuction
Prevention/elimination of mechanical complications	Compression Liposuction Plastic surgery
Reduction of accompanying obesity, if present	Exercise therapy Change in diet Guideline-compliant treatment of obesity (interdisciplinary)

8.1 **Complete decongestive therapy (CDT)**

To reduce edema and pain, physical therapy is performed in the form of complete decongestive therapy (CDT) (Földi 2005, Herpertz 2014, Szolnoky 2008 a, Szolnoky 2011, Reich-Schupke 2012). CDT includes the following:

a) Manual lymphatic drainage
b) Compression therapy
c) Exercise
d) Skin care

CDT involves an initial decongestive phase and a subsequent maintenance phase. If the patient also suffers from secondary lymphedema, the lymphedema guideline should be additionally followed (GDL 2009).

Particularly if the circumference is expected to drop under decongestive therapy, compression therapy should be performed with compression bandages in the decongestive phase and with compression stockings in the maintenance phase. In most cases, custom-made, flat-knitted stockings are required due to the shape of the limbs and the tissue properties. Circular-knit materials are only suitable in patients with mild lipedema.

To support, but not replace, manual lymphatic drainage (MLD) and compression, intermittent pneumatic compression (IPC) is also effective (Herpertz 1997, Szolnoky 2008 a).

CDT must be administered consistently. The intensity and frequency of the measures taken depend on the acuteness, severity, and duration of complaints, particularly the painfulness and degree of edema. If outpatient treatment cannot be successful, inpatient treatment is indicated.

The reduction of edema in the course of treatment should be documented by objective measurements (e.g., volumetry, circumference measurements). However, the extent of limb volume reduction by physical therapy is limited (Deri 1997). Reduction of the pathologically increased fat tissue with elimination of the disproportion is impossible with CDT.

8.2 **Liposuction**

Liposuction is used for the long-term reduction of pathological subcutaneous fat tissue at the legs and arms. It is particularly indicated if symptoms persist despite consistent conservative therapy or in case of progression of the findings (subcutaneous fat volume) and/or symptoms (pain, edema) (Cornely 2000, Schmeller 2014).

Due to the numerous advantages of this method, liposuction should be performed under tumescent local anesthesia (TLA), that is, using the “wet technique” with blunt microprobes (Klein 2000, Sattler 1997 and 2002, Rapprich 2002 and 2011, Cornely 2003 and 2006, Schmeller 2007). Supportive techniques such as vibration or water jet can be used as well (Stutz 2009). The procedure can be performed in an outpatient or inpatient setting (Schmeller 2012, Rapprich 2011, Cornely 2014). The indication must be established individually, taking into account patient-related factors.

Today, liposuction under tumescent local anesthesia is considered an established and low-risk surgical method (Langendoen 2009, Hanke 2003). Anatomic and clinical studies using lymphoscintigraphy and immunohistochemical examinations of the adipose tissue biopsy have shown that no relevant lymph vessel damage arises – which was not the case with the old “dry techniques” under general anesthesia (Frick 1999, Hoffmann 2004, Schmeller 2006, Stutz 2009, Bender 2007).

The procedure considerably improves spontaneous pain, pain on pressure, edema and ease of bruising, with significant differences found between the preoperative and postoperative situation (Rapprich 2011, Schmeller 2007 a and b, Schmeller 2012). It reduces and in some cases even eliminates the need for conservative therapy (Schmeller 2012, Rapprich 2011, Cornely 2014). In most patients, the improvement in findings persists for many years (Rapprich 2011, Baumgartner 2014, Schmeller 2012).

Furthermore, the reduction of the adipose tissue depots at the insides of thighs and knees reduces or eliminates the mechanical and occlusive skin damage. Correction of the axial alignment of the legs improves the patient’s mobility and gait (Stutz 2011) and reduces the risk of additional orthopedic complications resulting from the lipedema-associated pathological gait (e.g. gonarthrosis and coxarthrosis).

Surgeons experienced in liposuction recommend the treatment only where the indication has been critically established at a body weight > 120 kg (Schmeller 2014) or BMI > 32 kg/m^2 (Richter 2013). Morbid obesity accompanying lipedema should be treated before performing liposuction (DAG 2014). Ultimately, the establishment of the indication and performance of the liposuction are at the surgeon’s discretion. Liposuction is not a weight reduction method (Schmeller 2014). In case of severe lipedema or lipo-lymphedema, large, flaccid bags of tissue may remain following decongestive therapy and weight reduction; subsequent plastic surgery in the form of lymph-sparing dermolipectomy is more sensible than liposuction.

8.3 Nutrition, medication and physical activity

This part of the treatment concept is particularly important in case of concomitant obesity, which is found in more than half of lymphology patients (mixed population of lymphedema, lipedema, and lipo-lymphedema patients) (Lulay 2010, Reich-Schupke 2012).

a) Nutrition

Physical activity and a change in diet can reduce the excess weight but cannot eliminate the exclusively lipedema-related disproportionate excess fat tissue at the limbs.

In general, weight gain should be avoided or a normal weight should be achieved since overweight and obesity contribute to the edema component (Marshall 2008 a, 2008 b). According to the S3 guideline issued by the German Obesity Society, weight reduction is indicated at a BMI of 30 kg/m^2 or above or in case of a disorder that can be aggravated by overweight, such as lipedema. Weight reduction should always be based on a combination of nutritional, exercise, and behavioral therapy and include phases of weight reduction and long-term stabilization (DAG 2014, SIGN 2010, Söderlund 2009, NICE 2006, Wu 2009, Ross 2012).

There is no specific lipedema diet. Since high insulin levels promote lipogenesis and – via insulin resistance – also aggravate edema development, it seems sensible to avoid blood glucose and insulin spikes and allow ample time between meals (isoglycemic nutrition). The weight reduction should be achieved by reducing fat mass rather than muscle mass (Larsen 2010, Ebbeling 2012, Faerber 2014).

Among affected patients, many suffer from a variety of nutritional disorders (Stutz 2013). These patients should receive a change in diet with psychological support.

b) Drug therapy

Diuretic therapy is not indicated for eliminating leg edema in lipedema with or without secondary lymphedema. In high protein edema (e.g., lipedema, phlebedema, lymphedema), this therapy causes fluid removal from the interstitial space with consecutively increased protein content and hence secondary aggravation of edema (Herpertz 2014).

c) Physical activity

Exercising in water appears to be particularly effective (swimming, aqua jogging, aqua aerobics, aqua cycling) since the buoyancy relieves the joints, the water pressure causes lymph drainage, and the movement against the resistance of the water burns calories. Strength training alone is not very effective for weight reduction, with no equivalent evidence supporting it as in the case of endurance training (DAG 2014, Donnelly 2009, Church 2010, Slentz 2011).

8.4 Psychotherapy

Independently of the nutritional disorders mentioned above, many lipedema patients suffer from mental health problems (e.g. reduced self-esteem, reactive depression). Psychotherapy may be indicated in this context (Stutz 2013).

8.5 Summarizing evaluation of therapy

In summary, the combination of conservative and surgical therapies can achieve significant improvements in findings and alleviation of complaints. The initial treatment attempt should involve conservative measures. If complaints fail to improve, liposuction should be considered; in a considerable proportion of patients, liposuction can considerably reduce or even eliminate conservative therapy.

9. Information about this guideline

This guideline was written under the leadership of the German Society of Phlebology (Deutsche Gesellschaft für Phlebologie e.V. – DGP).

Other contributing specialist societies / professional associations:

- German Society of Lymphology (Deutsche Gesellschaft für Lymphologie – DGL)
- Professional Association of Lymphologists (Berufsverband der Lymphologen – BVL)
- Society of German-Speaking Lymphologists (Gesellschaft Deutschsprachiger Lymphologen – GDL)
- German Dermatological Society (Deutsche Dermatologische Gesellschaft – DDG)
- German Angiology Society – Vascular Medicine Society (Deutsche Gesellschaft für Angiologie – Gesellschaft für Gefäßmedizin e.V. – DGA)
- German Vascular Surgery and Vascular Medicine Society – Operative, Endovascular and Preventive Vascular Medicine Society (Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin – Gesellschaft für operative, endovaskuläre und präventive Gefäßmedizin e.V. – DGG)
- German Society of Plastic, Reconstructive, and Esthetic Surgeons (Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen – DGPRÄC)

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The statements in the guideline are based on current literature and clinical experience. The data available in the literature are based on only a few small, randomized controlled studies, some case series, and extensive expert knowledge. Detailed information on the methods used to generate the guideline is found in the methods report on the AMWF website (www.amwf.org/leitlinien/detail/II/037-012.html).

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