

AWMF register no.	037/012	Class:	S1

S1 Guideline Lipedema

ICD 10 R60.9 Edema, unspecified

Introduction

In daily clinical practice, questions constantly arise with respect to the diagnosis and treatment of lipedema. Often, there are also concurrent disorders of other diseases (e.g. lipedema and obesity, lipedema and lymphedema), where differential diagnosis is sometimes difficult.

For the diagnosis and treatment of lymphedema, please refer to the Society of German-speaking Lymphologists' guidelines (GDL) (GDL 2009). For the diagnosis and treatment of obesity, please refer to the German Obesity Society guidelines (DAG 2014).

The guideline presented focuses on the diagnosis and treatment of lipedema.

1. Definition

Lipedema is a chronic and progressive disorder that almost exclusively occurs in women and is characterized by a maldistribution of fat, noticeably disproportionate between the trunk and extremities. This is due to a defined, symmetrically localized increase in subcutaneous fatty tissue of the lower and/or upper extremities (Herpertz 1997). In addition, there is edema, which is worsened by orthostasis, as well as a tendency to hematoma following trivial traumas (Allen 1940, Wienert 1991, Herpertz 2014). It is also characterized by increased pressure tenderness; usually accompanied by spontaneous pain.

2. Synonyms

The following terms are often used as synonyms. There is still debate as to whether they actually describe the same clinical picture: Lipomatosis dolorosa, lipohypertrophy dolorosa, adiposis dolorosa, lipalgia, adiposalgia, painful column leg, painful lipedema syndrome, lipohyperplasia dolorosa.

3. Occurrence

The disease occurs almost exclusively in women. Lipedema usually starts during a period of hormonal change such as puberty, pregnancy or menopause.

In men, lipedema-type changes have only been reported during hormonally active treatment, pronounced hormonal disorders (e.g. hypogonadism) or with liver cirrhosis (Weissleder 2011, Wold 1951, Child 2010, Chen, 2004).

There exists no adequate data from large-scale studies with respect to epidemiology. Dependent on the collective and diagnostic criteria studies, the majority of outpatient studies resulted in a frequency of 7-9.7% (Földi 2007, Marshall 2011, Miller, 2008); but significantly smaller values were also noted (0.1%) (Herpertz 2014). Examinations carried out on inpatients in specialist lymphology clinics accounted for between 8% and 18% (Herpertz 1997, Meier-Vollrath 2005, Lulay 2010).

Overall, in the light of widespread uncertainty with respect to diagnosis, this has resulted in a high number of unreported cases. However, there are also patients who are mistakenly diagnosed with lipedema, although they have not fulfilled the criteria for lipedema.

4. Etiopathogenesis

The etiology is still unknown. The exact pathomechanisms and special role of hormones and their receptors are also unclear (Szel 2014). A genetic component with a family cluster of lipedema is characteristic in up to 60% of cases (Greer 1974, Wold 1949, Harwood 1996, Fife 2010). E.g. An autosomal dominant inheritance pattern with incomplete penetrance was detected in six families with lipedema over three generations (Child 2010).

The defined proliferation of fatty tissue is the result of hypertrophy and hyperplasia of fat cells (Kaiserling 2005). In addition, changes in connective tissue have been observed (Brenner 2009). Moreover, there is the existence of a capillary permeability disorder (Weissleder 1997), where more and more liquid from the vascular system collects in the interstitium. This increased capillary fragility results in noticeable susceptibility to hematoma (Szolnoky 2008b).

Due to the increased quantity of fluid, the still intact lymphatic system responds with increased lymphatic transport (Brauer 2005). Whether the constant load of lymphatic vessels leads to degenerative changes in the vessel wall with a resulting reduction of

transport capacity (high volume transport insufficiency), is hypothetical. When the lymph, predominantly in the dependent body parts, is no longer able to be sufficiently transported, it results in edema. Over several years, an increase in subcutaneous fat and edema may occur.

In addition, a delayed and diminished veno-arterial reflex (VAR) can be found where there is lipedema with orthostasis. Disorders of the VAR promote orthostatic edema. This disorder can be significantly improved by use of a compression bandage (Strößenreuther 2001).

In a proportion of cases it later develops into lipedema with secondary lymphedema (so-called lipolymphedema), not always with positive Stemmer signs. In its advanced stages, secondary changes can be seen, such as sclerosis and papillomatosis through fibroblast proliferation in the dermis. Progressive fibrosis of subcutaneous fatty tissue results in mechanical failure (Földi 2005, Brauer 2002, Brauer 2005).

The histological changes in lipedema are not pathognomonic. In addition to increased, and sometimes hypertrophied fat cells, a high level of capillary blood vessels can be seen in the interstitium; perivascularly macrophages, fibroblasts, mast cells, as well as some fatty tissue necrosis can be found. In the late stage of the disease, the fibrotic portion increases (Kaiserling 2005). Immuno-histochemical investigations indicate degenerative and regenerative fatty tissue changes, characterized by crown-like structures from necrotic adipocytes surrounded by infiltrating CD68 + macrophages and the proliferation of stem cells/progenitor cells and connective tissue cells (Ki67 and CD34 positive). These findings support the thesis of enhanced adipogenesis in lipodemic tissue (Suga 2009).

5. Clinical examination and follow-up:

Changes in lipedema always occur symmetrically on the legs and/or arms (Herpertz 2004, Cornely 2002). The proliferation of fat distributes homogeneously over the upper and/or lower legs ("pillar leg") or upper and/or lower arms (**table 1**). Typically the change in diameter can be distinguished from the adjacent healthy areas ("Muff", "Türkenhosen phenomenon", "collar formation").

Table 1: Lipedema distribution according to localization (mod. acc. to Herpertz 2014).

Legs	Arms
Upper leg type	Upper arm type
Full leg type	Full arm type
Lower leg type	Lower arm type

There are also often concurrent disorders within one person. Solitary lipedema of the arm without spreading to the legs is extremely rare.

Later bulge formations may also occur (dewlaps), which are mainly located on the inner sides of the upper leg and knee, rarely also in the ankle area. Friction results in tissue trauma (chronic irritant dermatitis), and occlusion effects result in maceration of the skin folds and consecutive infections. The bulge formations on the inside of the upper leg also cause disturbance in gait with axis misalignment of the legs and orthopedic complications (mainly valgus gonarthrosis) (Stutz 2009).

Those affected are often severely constrained in their quality of life. This is due, on the one hand, to volume increase and disproportion between trunk and extremities, and on the other hand, those affected suffer with feelings of tension and pain on movement and localized tenderness - which increases in warm weather, after sitting or standing for a long time and in the evenings. Sometimes significant spontaneous pain may also occur. The pain is described mainly as dull, pressured and heavy (Schmeller 2008).

The disease is a chronic progressive illness. Lipedema is differentiated into three morphological stages (Fife 2010, Meier-Vollrath 2004) (**table 2**). Progress is unpredictable and varies in individuals. The division of stages is not necessarily linked to the extent of clinical symptoms (pain).

Table 2: Classification of lipedema <u>according to morphology</u>. The changes are possible on both arms and legs.

Stage	Characteristics
1	Smooth skin surface with evenly thickened, uniformly impressive subcutis
2	Uneven, mostly wavy skin surface, knotted structures in a thickened subcutaneous area
3.	Pronounced circumferential growth with overhanging tissue parts (formation of dewlap)

A progression to lipedema with secondary lymphedema can occur at any stage - partly depending on comorbidities (e.g. obesity, inactivity) - (Fall 2012). Accompanying existing obesity can worsen the course and the clinical picture of the lipedema (Marshall 2008 a).

6. Diagnostics:

Early diagnosis of lipedema through clinical history, examination and palpation, based on typical characteristics should be aimed for (Forner-Cordero 2012, **Table 3**). Other causes of edema should be excluded. For this purpose, additional diagnostic measures may be required.

It is also recommended to document parameters such as weight, body-mass index (BMI), "waist-hip ratio" (WHR), and "waist-height ratio" (WTR) as a follow-up, as well as circumference and volume measurements of the extremities and the daily activity index. In particular, in difficult cases of differential diagnosis (obesity versus lipedema), where there is increase in volume of the extremities despite reduction in total weight, these follow-up parameters can be helpful for the diagnosis of lipedema (Dutch society for Dermatology 2014).

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

Lipedema:

Begins with puberty, pregnancy or menopause

Disproportionate fat tissue proliferation (extremities- trunk)

Collar or muff formation in the joint regions

Hands and feet are not affected

The affected limbs feel tight and heavy

Tenderness on palpation or spontaneously - increasing during the course of the day

Edema – increasing during the course of the day

Tendency to hematoma

Stemmer's sign negative.

For quantitative evaluation of subcutaneous fatty tissue, and for follow-up - morphological methods can be used. The collected findings are, however, not specific (especially when differentiating with symmetric lipohypertrophia). So a homogeneous proliferation of the subcutis is depicted by means of high-resolution sonography, and at the same time, an evenly increasing echogenicity and hyperechoic septa in the absence of non-echoing crevices (Marshall 1996). Nonspecific thickening of the subcutis can also be detected using computer tomography (Vaughan 1990, Werner 1993) and magnetic resonance imaging (Duewell 1992, Dimakakos 1997), however can not be used as evidence for the diagnosis.

Morphological studies of the lymphatic system by indirect lymphography show typical, but not pathognomonic changes in the form of feathered or flame type deposits of contrast agent (Partsch 1988, Tiedjen 1992, Weissleder 1997).

Using fluorescence micro-lymphography micro-aneurysms can be found (Amann-Vesti 2001& 2002). Fluorescence micro-lymphangiography can be carried out using fluorescence-marked dextran or indocyanine green (Amann-Vesti 2001, Schingale 2013).

Functional tests of the lymphatic system were carried out using standardized (static and dynamic) functional lymph scintigraphy (Bilancini 1995, Brauer 2000 & 2002, Harwood 1996, Weissleder 1995, Boursier, 2004). While there were no conspicuous changes (Bräutigam 1998), in the early stages of the disease, increased lymph transport (high volume transport insufficiency) and in the later stages of the disease prolonged transport time, can be partially seen with pathological lymph uptake values (Brauer 2005).

The above functional examinations and imaging are not necessary as part of a clinical routine for the diagnosis of lipedema. They can be useful however for differential diagnosis and scientific queries, as well as for follow-up checks.

7. Differential diagnoses

The major differential diagnoses are presented in the form of two tables (table 4 and table 5).

Table 4: Typical clinical features for the demarcation of lipedema, lipohypertrophy, obesity and lymphedema.

	Lipedema	Lipohypertrophy	Obesity	Lymphedema
Excessive fat	+++	+++	+++	(+)
Disproportion	+++	+++	(+)	+
Edema *.	+++	Ø	(+)	+++
Pressure pain	+++	Ø	Ø	Ø
Tendency to hematoma	+++	(+)	Ø	Ø

Explanation of symbols:

⁺ to +++ present; (+) possible; Ø not present

^{*} Characteristic edema is variable and dependent on the degree of previous treatment, as well as the stage of the disease.

Table 5: Other differential diagnoses including treatment options (mod. acc. to Miller 2014). Intermittent pneumatic compression therapy (IPC) is carried out in addition to MLD as appropriate, never as a replacement.

Diagnosis	Symptoms	Treatment options		
Lipedema	Symmetrically located, focussed on the extremities, disproportional pain, tendency to hematoma, local edema, orthostatically aggravated	Compression MLD (manual lymphatic drainage) IPC (Intermittent pneumatic compression therapy) liposuction		
Lymphedema	Edema, usually includes feet/hands, stage dependent induration / fibrosis, usually positive Stemmer's sign, papillomatosis cutis, lymph cysts, lymph fistulas	MLD Compression Movement with compression IPC Skin care Breathing exercises		
Lipedema with secondary lymphedema	Symmetrically located, focussed on the extremities, disproportional Pain Tendency to hematoma Local edema, orthostatically aggravated edema of the hands or feet, Stemmer's sign positive Secondary lymphedema changes (see above)	MLD Compression Movement with compression IPC Skin care Breathing exercises and liposuction		
Lipedema with accompanying obesity	Concurrent disorder lipedema and obesity see above & below	Weight loss Compression MLD IPC Only after weight loss Liposuction		
Phlebedema	Edema of the legs/arms CVI skin signs:Stasis dermatitis, hyperpigmentation, dermatosclerosis, phlebectasia, corona phlebectatica, atrophy blanche, ulceration	Compresion IPC Restructuring of varicose veins		
Lipohypertrophy	Localized lipohypertrophy	Liposuction		
Obesity	Generalized lipohypertrophy	Weight reduction		
Obesity with secondary edema (obesity edema)	Generalized lipohypertrophy with secondary edema	Weight loss 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		

8. Treatment

Treatment has two aims:

- a) The elimination or improvement of the findings and symptoms (in particular pain, edema and disproportion, **table 6**).
- b) Prevention of complications. With advanced and severe cases, especially with increased leg volume, there is an increased risk of dermatological (e.g. maceration, infections), lymphatic (e.g. erysipelas, lymphedema) and orthopedic complications (gait disturbance, axle misalignment).

No causal treatment is known. Symptomatic effective measures (8.1-8.4) are carried out according to stage and are individualized.

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

Aim of treatment	Therapeutic measures
Edema reduction	Compression MLD (manual lymphatic drainage) IPC (Intermittent pneumatic compression therapy)
	Movement
	Liposuction
Pain relief	Compression
	MLD
	IPC
	Liposuction
Reducing tendency to hematoma	MLD
	IPC
	Liposuction
Reduction of the pathologically	Liposuction
increased subcutaneous fat	
Prevention/removal of mechanical	Compression Liposuction
complications	Plastic surgery procedures
Reduction of accompanying obesity	Movement therapy Nutrition
	Guideline-oriented treatment of obesity (interdisciplinary)

8.1 Combined physical decongestion therapy (CPDT)

For edema and pain reduction, physical measures are implemented in the form of combined physical decongestion therapy (CPDT) (Földi 2005, Herpertz 2014, Szolnoky 2008 a, Szolnoky 2011, Reich-Schupke 2012). This includes:

- a) manual lymphatic drainage,
- b) compression therapy,
- c) movement therapy and
- d) skin care.

CPDT is divided into an initial decongestion and a subsequent maintenance period. For additional secondary lymphedema, the guidelines for lymphedema should additionally be followed (GDL 2009).

Compression therapy should follow - for expected circumference reduction with decongestive measures - in the congestion phase with bandages, in the retention phase with compression stockings. In the majority of cases, due to limb shape and tissue composition, the stockings need to be made to measure. Tubular fabrics are suitable only for a diagnosis of mild lipedema.

Intermittent pneumatic compression (IPC) is also effective for supporting - but not replacing manual lymphatic drainage (MLD) and compression (Herpertz 1997, Szolnoky 2008 a).

CPDT must be applied consistently. Intensity and frequency of the measures is dependent on the acuity, level of severity and duration of the condition, especially pain and degree of edema. If outpatient therapy is unsuccessful, treatment should be carried out as an inpatient.

Edema reduction therapy should be documented using objective measurement techniques (e.g. volumetry, circumference measurements). Reduction of limb volume using physical measures is however limited (Deri 1997). A reduction of pathologically increased adipose tissue and eliminating disproportion is not possible with CPDT.

8.2 Liposuction

Liposuction is used for the permanent reduction of abnormal subcutaneous fat on the arms and legs. It is especially indicated when despite consistently carried out conservative therapy, symptoms still remain or there is a progression of findings (subcutaneous fat volume) and/or symptoms (pain, edema) (Cornely 2000, Schmeller 2014).

Due to its many advantages, liposuction should be carried out using tumescence local anaesthesia (TLA), i.e. a "wet technique" with blunt micro-probes (Klein 2000, Sattler 1997 & 2002, Rapprich 2002 & 2011, Cornely 2003 & 2006, Schmeller 2007). Supporting techniques such as vibration or water jets can also be used (Stutz 2009). This procedure can be carried out as an outpatient or inpatient (Schmeller 2012, Rapprich 2011, Cornely 2014). The indication must take into account individual patient factors.

Nowadays, liposuction using tumescent local anesthesia is an established and low-risk surgical method (Langendoen 2009, Hanke 2003). Anatomical and clinical studies, have been able to prove, based on lymph scintigraphy and immuno-histo-chemical investigations of fatty tissue aspirates, that - unlike with previous procedures using general anesthesia with "dry techniques" - no relevant damage to the lymphatic vessels occurs (Frick 1999, Hoffmann 2004, Schmeller 2006, Stutz 2009, Bender 2007).

The procedure leads to pronounced improvements of spontaneous pain, pressure pain, edema and tendency to hematoma, with significant differences pre and post operatively (Rapprich 2011, Schmeller 2007 a and b, Schmeller 2012). A reduction of conservative therapy, and sometimes even freedom from therapy, is achieved (Schmeller 2012, Rapprich 2011, Cornely 2014). Improvement remains for several years (Rapprich 2011, Baumgartner 2014, Schmeller 2012).

Furthermore, due to the reduction of fatty tissue deposits on the inner sides of the upper leg and knee, mechanical and occlusive related skin damage is reduced or eliminated. Correction of leg deformity leads to improvement of movement and gait (Stutz 2011), as well as risk reduction for further orthopedic complications as a consequence of lipedema-associated pathological gait (e.g. gonarthrosis and coxarthrosis).

As a result of reduction in symptoms, increased mobility, less time spent on conservative therapy and regained confidence, the quality of life of those affected is greatly improved.

For liposuction, experienced surgeons determine a critical indication for body weight > 120 kg (Schmeller 2014) or a BMI > 32 kg/m² (Richter 2013). Morbid obesity existing in parallel to the lipedema should be addressed prior to liposuction treatment (DAG 2014). Ultimately, indication determination and the carrying out of the liposuction is at the discretion of the surgeon. Liposuction is not a method for weight loss (Schmeller 2014). For pronounced lipedema or lipolymphedema, large, sagging tissue sacks may remain after successful decongestion and weight loss, for which subsequent plastic surgery in the form of dermolipectomy, while protecting the lymphatic vessels, is preferable to liposuction.

8.3 Nutrition, medication, and physical activity

This part of the treatment concept is particularly important for co-existing obesity, which is the case for over half of lymphology clients (collective mix lymphedema, lipedema, and lipolymphedema) (Lulay 2010, Reich - Schupke 2012).

a) Nutrition

Physical activity and nutritional changes can help reduce weight, but are unable to eliminate the lipedema-related disproportionate fatty tissue increase of extremities.

In principle weight gain should be avoided and normal weight adhered to, because obesity and being overweight, for example, contribute to a worsening of edema (Marshall 2008 a, 2008b). Indications for weight loss, according to the S3 guideline of the German Obesity Society, are a BMI of over 30 kg/m2 or a condition that may be aggravated by obesity, as is the case with lipedema. Weight reduction should always be based on a combination of nutrition, sport, and if necessary, behavioral measures, and should include stages of weight loss as well as long-term stabilization (DAG 2014, SIGN 2010, Södlerlund 2009, NICE 2006, Wu 2009, Ross 2012).

There is no specific lipedema diet. High insulin levels promote lipogenesis, and insulin resistance also increases the formation of edema, a diet which prevents blood sugar and insulin spikes and which has adequate and sufficient breaks between meals is recommended (isoglycemic nutrition). Care should be taken that weight loss does not burden muscle mass and fat mass (Larsen 2010, Ebbeling 2012, Faerber 2014).

In addition, a high proportion of patients with various eating disorders can be found amongst those affected (Stutz 2013). For this reason, a change of diet should be accompanied by psychological support.

b) Drug therapy:

Diuretic therapy for the removal of leg edema in lipedema, with or without secondary lymphedema, is not indicated. Protein-rich edema (e.g. phlebolymphedema, lipedema, lymphedema) results in removal of fluid from the interstitium with consecutively increased protein content and therefore is secondary to reinforcement of the edema (Herpertz 2014).

c) Physical activity

Sporting activities, especially those in water, are particularly effective (swimming, aquajogging, aqua-aerobics, aqua-cycling), as the joints are lighter due to the buoyancy, lymph drainage is carried out due to the water pressure, and calories are used up as a result of movement against the resistance of the water. Strength training alone has little effect for weight loss, there is no comparable data for endurance training (DAG 2014, Donnelly 2009, Church 2010 Slentz 2011).

8.4 Psychotherapy

Independent of the above-mentioned eating disorders, many lipedema patients suffer from psychological problems (e.g., reduced self-esteem, reactive depression). Here, appropriate psychotherapy is indicated (Stutz 2013).

8.5. Overall assessment of treatment

In summary, it can be said that a combination of conservative and operative treatment measures enables a distinct improvement in symptoms and results. Primarily, treatment should be carried out using conservative measures. If there is an improvement in symptoms, then liposuction can be considered; as a result, conservative therapy can be reduced or sometimes even completely waived in a substantial number of those affected.

9. Information on this guideline

The creation of the guideline was carried out under the auspices of the German society of Phlebology e.V. (DGP).

Other professional societies involved:

- Society of German Lymphologists (GDL)
- German Dermatological Society (DDG)
- German society for Angiology Society for Vascular Medicine (DGA)
- German Society for Vascular Surgery and Vascular Medicine Society for Operative,
 Endovascular and Preventive Vascular Med (DGG)
- German Society of Plastic, Reconstructive and Esthetic Surgeons (DGPRÄC)

The primary work group / steering group consisted of the following 10 members (in alphabetical order):

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The versions of the guideline are based on the status of current literature and clinical experience. The scientific knowledge in the literature is dominated by only a few small randomized controlled trials, some case studies, and extensive expert knowledge. Detailed sector-specific information on the methodology of guideline creation can be found in the method report on the AWMF website (www.awmf.org/leitlinien/detail/ll/037-012.html).

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Annex

Declaration of conflict of interest according to authors' own statements (list of authors in alphabetical order)

Name	Consultant or reviewer, or paid work as part of a scientific advisory board of a sub company of a health company (e.g. pharmace utical industry, medicinal products industry), a commerci ally-oriented research organizati on or insurance company	Fees for lecture s and teachin g or paid author or co- authors hips on behalf of a health compa ny, a comme rcially oriente d scientifi c organiz ation or insuran ce compa ny	Financial donations (third-party) for research projects or direct financing of employees on behalf of a health company, a commercially-oriented scientific organization or an insurance company	Owner interest of drugs/ medical product s (e.g. patent, copyrig ht, sales license)	Owners hip of stocks and shares, investm ents with involvin g health compan ies	Person al econo mic relation ship to an authori zed represe ntative of a health company of health	Member of specialist companies /professiona I bodies, with respect to guideline developmen t, elected official with respect to guideline developmen t	Politic al, acade mic (e.g. affiliati on to specifi c "schoo Is"), scientific or person al interes ts that could constitute a possible conflict	Current employer, relevant employer within the last 3 years
Brauer, Wolfgang J; Dr.	Teaching at the Centre for Manual Lymph Drainage; lecturer on lympholog y, lymphologi cs for doctors course.	no	no	no	no	no	DGL, GDL	no	Emmendin gen Hospital until Sept./2012; since then retired with minimal employmen t at Przetak practice, Freiburg
Cor nel y, Ma nue I; Pro f. Dr.	no	no	no	no	CG- lymp h; speci alist clinic oper ative of whic h lymp holo gy 52%	no	Founding President of the Professional Association of Lymphologis ts	no	self- employed
Faer ber, Gabri el; Dr.	Transla tion editing for Protein S.A. Luxembu rg	no	no	no	no	no	DGP	no	self- employed

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Ure, Christian; Dr.	no	Servie r (Daflo n) Phleb ology advan ced trainin g for doctor s "Meeti ng point vein disord ers"	no	no	no	no	GDL	no	Distric t Hospit al Wolfs berg, KABE G

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