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Lipoedema Guidelines

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1 Aetiopathogenesis, Pathophysiology, Painful Symptoms

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1.1 Definition

Recommendation 1.1

	Degree of recommendation	Consensus
Lipoedema **shall** be described as a painful, disproportional, symmetrical disorder of adipose tissue distribution in the limbs, encountered almost exclusively in women.	↑↑	Strong consensus (100%)

- Lipoedema is always painful. Painless disproportional, symmetrical disorder of adipose tissue distribution is defined as lipohypertrophy, and is not covered by these Guidelines.
- Lipoedema is a disproportional disorder of adipose tissue distribution that affects only the limbs. Head, neck and trunk are not affected.
- Lipoedema is a symmetrical disorder of adipose tissue distribution in the limbs. It affects both hips, both thighs, both lower legs, etc. symmetrically. In the upper limbs, it affects both shoulder regions, both upper arms or both lower arms. The feet and hands are not affected.
- Lipoedema is not caused by obesity, nor does it cause obesity.
- Obesity may occur coincidentally, as in all women. However, this coincident obesity is proportional, affecting the trunk also.
- Obesity-related lymhoedema may arise from this coincident obesity. This affects principally the lower limbs.
- Orthostatic congestions may occur, as in all women. However, these are independent of the lipoedema.

1.2 Historical outline

The first publication by Edgar V. Allen and Edgar A. Hines 1940 (Allen and Hines 1940) lists the following characteristics:

- Lipoedema affects women (almost) exclusively.
- The principal complaint is a swelling of the adipose tissue of the legs, which has existed for many years and in some cases can be traced back to girlhood.
- Lipoedema does not generally affect the feet.
- Augmentation of the limbs is generalised and symmetrical.
- The disease is usually associated with an increase in body weight.
- There are neither current nor historical repeated episodes of acute cellulitis (erysipelas).
- Swelling below the knee is accentuated if the patient spends a lot of time on her feet and in warm weather.
- Leg pain is an everyday occurrence.
- In many cases there is a previous history of a similar condition in other family members.

Patients are normally very sensitive about the appearance of their limbs. This is probably an indication of emotional and physical distress.
The patient occasionally has the feeling that her outsized legs have "ruined her life". Many are "ashamed" of their legs.

In a later article published with Lester E. Wold, Allen and Hines state that: (1) the size and configuration of the feet are usually normal; (2) there is regular to high sensitivity to finger pressure;

and (3), especially at the end of the day, there may be some indications of oedema in the legs (Wold et al. 1951). Furthermore, the authors describe the skin and subcutaneous fat as soft and malleable. There may be generalised adiposity, but in most cases the upper body and limbs are of “normal” size and shape.

The information reported by the original authors has been extended by descriptions of the disease in the patients’ arms; in up to 90% of cases a – likewise symmetrical – innate disorder of the fat distribution arises simultaneously with that in the legs (Ghaben and Scherer 2019; Vishvanath and Gupta 2019; White and Ravussin 2019).

1.3 Possible Causes

1.3.1 Female Sex

Ever since the first description by Allen and Hines (Allen and Hines 1940), the literature has been virtually unanimous that in practice lipoedema affects only women. This could give rise to two basic possible pathogenetic factors:

1) Disorder of the X-chromosome, and
2) Disorder of a specific female hormone.

1.1 Genetics

Men are extremely seldom affected by lipoedema; only a few individual cases are reported in the literature. In general, it is assumed that excessive hormone disorder is responsible for the development of the male form of lipoedema; although there are also reports of cases where no such hormone disorder exists (Bertlich et al. 2021; Chen et al. 2004).

In a family with cases of lipoedema over three generations, where the subject’s mother, three sisters and a niece were affected, Child et al. performed a linkage analysis with X chromosome markers and excluded the X chromosome with all the markers (Child et al. 2010). The authors concluded that autosomal-dominant inheritance was the most probable inheritance mechanism.

In a literature analysis, Paolacci et al. (2019) identified some possible candidates for an ideal diagnostic gene test for genetically conditioned subcutaneous fat accumulations like lipoedema.

The first evidence for a genetic basis indicated a missense variant in AKR1C1 [p.(Leu213Gln)], the gene that codes for aldo-keto reductase; this catalyses the inactivation of progesterone to its inactive form (Michelini et al. 2020). The analyses point to partial loss of function in the variant.

The analysis performed by Grigoriadis et al. (2022) yielded genetic loci associated with the lipoedema phenotype, supported by an independent cohort from the 100,000 Genomes Project. The most important SNP rs1409440 is found upstream of LHFPL6, from which it is assumed that it plays a role in lipoma formation. How exactly this is related with lipoedema has not yet been explained.

1.4 Morphology and Function

Lipoedema patients (L) present a significantly thicker epidermis than a BMI-matched control group (C) (L: 126.1 ± 20.2 µm vs. C: 79.3 ± 15.9 µm; $p < 0.001$) (Felmerer et al. 2020a).[1]

The Kaposi-Stemmer sign on the toes is negative (Brauer et al. 2015), but may become positive if in addition to the lipoedema the patient presents with [obesity-associated] lymphoedema (Ghods 2021). Beltran and Herbst (2017) found further that the proportion of patients (BMI: 39 kg/m² ± 12 kg/m²) with positive Kaposi-Stemmer sign increases with the stage of the disease.

The subcutaneous tissue of lipoedema patients is clearly less compressible: a compressibility of less than 10% with a standardised weight is a clear indicator of lipoedema (Kasseroller and Brenner 2019); however, there are contradictory data. In a broader study, in which however no standardised

compression was applied, no correlation was found (Hirsch et al. 2018).

The proportion of women with hypermobile joints (Beighton Score ≥ 5) is clearly higher in lipoedema patients (BMI: 39 kg/m² ± 12 kg/m²) than in patients with M. Dercum (BMI: 33 kg/m² ± 8 kg/m²) (Beltran and Herbst 2017); furthermore, this proportion increases with the lipoedema stage (Stage 1: 26.9%, Stage 2: 59.5%, Stage 3: 66.7%).

Lipoedema patients present microaneurysms of the initial lymph vessels in the thigh and ankle region more often than obese patients (Amann-Vesti et al. 2001). Microaneurysms were defined by the authors as an initial lymph vessel with more than twice the minimum diameter of the vessel. The intravascular pressure in the initial lymph vessels is still normal (Amann-Vesti et al. 2002). Lipoedema patients present an abnormal lymphoscintigraphy pattern with slowing of the lymph flow, pointing to analogies with the alterations found in patients with lymphoedema (Bilancini et al. 1995; Boursier et al. 2004). Young lipoedema patients present a higher than normal transport function by the lymph system, while older patients present a clearly lower function (Brauer and Brauer 2005). Reduced transport capacity correlates significantly with the duration of the symptoms, but not with the body fat mass or the morphological stage (Buso et al. 2022). Lymph vessels in the lower limbs of Stage I and II lipoedema patients examined by fluorescence lymphograpy appear dilated, with intravasal pooling, in comparison with controls matched for BMI and age; however, their drainage performance is significantly stronger than that of the controls (Rasmussen et al. 2022). Furthermore, lipoedema patients present a higher systemic level of VEGF-C (control group of BMI-matched patients; $p = 0.02$), which increases vessel permeability and interstitial fluid; surprisingly, no morphological alterations were observed in the lymph vessels despite the high VEGF-C levels (Felmerer et al. 2020b).

Szél and Szolnoky described microangiopathy as an early histological sign of lipoedema (Szél et al. 2014; Szolnoky et al. 2008), which may possibly be attributed to a primary defect of the endothelial barrier function. Microangiopathy is neither specific nor pathognomonic. Alternatively, hypoxia may cause increased fragility of the capillaries. Increased free fatty acid contents (Kim et al. 2005; Vigili de Kreutzenberg et al. 2000) may lead to endothelial dysfunction and altered transendothelial transport. In a low acid environment, HIF-1A-induced fibrosis may develop (Halberg et al. 2009).

BMI is not a suitable parameter for selection of the control group, since the BMI in lipoedema patients is fundamentally higher than in healthy subjects, so matching for BMI favours obese patients.

Apart from hypoxia, there are two other effects that may be related with the appearance of microangiopathy: obese hyperplasia and local high blood pressure in the capillaries, which leads to hyperpermeability (Szél et al. 2014).

Propensity to bruising, which has frequently been reported, is attributable to microangiopathy; however, there is no connection between the bleeding tendency of lipoedema patients and defective coagulation (Sucker et al. 2021).

The relative permittivity of the tissue in lipoedema patients is comparable with that of healthy patients (Birkballe et al. 2014).

Patients with lipoedema present increased cerebral blood-flow compared to healthy subjects (Petersen et al. 2020).

Lipoedema patients present a larger atrium and left ventricle and a greater ejection fraction from the left ventricle than the control group, with no significant differences in other variables measured by echocardiography (Nemes et al. 2020).

Investigation by bio-impedance spectroscopy, as a surrogate for measuring fluid content, found reduced impedance in the arms and legs of patients as their lipoedema stage increased (Crescenzi et al. 2019). Impedance values were always markedly higher in the arms than in the legs. The impedance values in the arms of the healthy control group were found to be in the region of those of patients with Stage 2 lipoedema. In contrast, the impedance values in the legs of the control group were scarcely higher than those of patients with Stage 1.

The sodium content in the tissues of lipoedema patients, measured by sodium MRI, is significantly higher than that of BMI-matched controls in the lower limbs, but not in the arms (Crescenzi et al. 2020; Crescenzi et al. 2018)

Several studies have shown that lipoedema-affected adipose tissue is fibrotic and strongly vascularised with enlarged blood vessels; in normal-weight patients it is infiltrated by macrophages and hypertrophic adipocytes (Al-Ghadban et al. 2019; Child et al. 2010; Precone et al. 2019). Furthermore, there is increased proliferation of stem, progenitor and stromal cells in the adipose tissue of lipoedema patients (preadipocytes, $Ki67^+$ cells and $CD34^+$ cells) (Al-Ghadban et al. 2019; Suga et al. 2009; Taylor et al. 2004).

Lipoedema patients present significantly larger adipocytes than a BMI-matched control group (BMI: L: 27.16 kg/m² ± 2.19 kg/m² vs. C: 28.29 kg/m² ± 3.93 kg/m²; area of adipocytes: L: 12.250 ± 2.095 µm² vs. C: 7.389 ± 1.920 µm²; $p < 0.001$; diameter of adipocytes: L: 415 ± 50.3 µm vs. C: 309 ± 37 µm; $p < 0.001$) (Felmerer et al. 2020a).

Overall, there is an increase in $CD45^+$ cell infiltration (CD45: common leukocyte antigen) compared with a BMI-matched control group. On the other hand, there is no change in the number of $CD3^+$ cells (T-cell compartment), but a significant increase in $CD68^+$ macrophages (Felmerer et al. 2020a). The increased infiltration of immune cells, and especially the predominance of macrophages, agrees with the results of other studies (Al-Ghadban et al. 2019), which make a clear distinction between lipoedema and lymphoedema (Gousopoulos et al. 2016a; Gousopoulos et al. 2016b). Data from Wolf et al. (2022) indicate clearly that lipoedema causes a shift of macrophages in the adipose tissue towards an immunosuppressive state (M2).

Stromal and stem cells obtained from lipoedema patients by liposuction, presumably preadipocytes, present increased numbers of $CD146^+$ endothelial cells/pericytes compared to healthy subjects (Priglinger et al. 2017). From this it may be concluded that this increase could be a marker for permeable blood and lymph vessels in the adipose tissue of the lipoedema. This shows the spread of the adipose tissues in lipoedema, by means of an increase in the size of adipocytes (hypertrophy) and/or the proliferation (hyperplasia) and differentiation (adipogenesis) of adipose precursor cells/preadipocytes into mature adipocytes.

Stem cells obtained from lipoedema patients show impaired adipogenesis from early stages of differentiation *in vitro*. In parallel with a severely reduced cytoplasmatic accumulation of lipids, the higher stages of lipoedema stem cells and adipocytes from lipoedema adipose tissue present significantly smaller quantities of adiponectin and leptin in comparison with control cells. Furthermore, there are differences between lipoedema cells and non-lipoedema cells in terms not only of their expression of insulin-like growth factor-1, aromatase (CYP19A1) and interleukin-8, but also in their proliferative activity (Bauer et al. 2019b)

Small, extracellular vesicles of the stromal vascular fraction (SVF) of lipoedematous adipose tissue from three patients showed different regulation of micro-RNAs (^RNA; miR-16-5p, miR-29a-3p, miR-24-3p, miR-454-p, miR-144-5p, miR-130a-3p, let-7c-5p) compared with healthy tissue (Priglinger et al. 2020).

Any differences found may be attributable to several factors, including the use of different techniques to investigate proliferation and differentiation, different liposuction techniques and different sites for collection of sample tissues; the stage of the disease reached in the patients selected for the study may also have an effect.

1.5 Pathophysiology

Lipoedema patients (n = 10) present abnormal interchange of lipids compared to a BMI-matched control group (n=11) (Felmerer et al. 2020a), but not compared to a random sample from the general population (Sanchez-De la Torre et al. 2018):

- Total cholesterol is high, but still within the physiological range.
- LDL (low-density lipoprotein) is high, but still within the physiological range.
- Triglycerides are high, but still within the physiological range.
- Apolipoprotein is high, but still within the physiological range.

Four prevalent adipokines (IL-6, IL-18, lipocalin-2, leptin) present no significant alterations (Felmerer et al. 2020a). These adipokines are high in obese individuals (Esposito et al. 2002; Friedman and Halaas 1998; Ouchi et al. 2011; Wang et al. 2007; Ziccardi et al. 2002), marking a clear distinction between lipoedema and obesity (Felmerer et al. 2020a).

An altered gene signature is found, with overregulation of various pro-adipogenic and anti-adipogenic genes, while the expression of other typical adipose tissue genes remains unchanged (Felmerer et al. 2020a). One of the differentially expressed genes was overregulated in lipoedema patients (CCND1: 2.16-fold increase, $p = 0.016$), while all the others were downregulated (CCAAT enhancer-binding protein delta [C/EBP-6]: 2.7-fold decrease, $p < 0.001$; CFD: 1.88-fold decrease, $p= 0.01$; NCOR2: 1.81-fold decrease, $p = 0.037$; Krüppel-like factor 4 (KLF4): 3.57-fold decrease, $p= 0.01$). Leptin gene expression is also overregulated in adipocytes in the subcutaneous layer of the thigh of lipoedema patients (Al-Ghadban et al. 2020). PPAR-γ expression was significantly higher in adipocytes differentiated from stem cells obtained from the abdominal adipose tissue of lipoedema patients than the corresponding cells from healthy subjects ($p = 0.03$) (Al-Ghadban et al. 2020).

C/EBP-δ is a transcription factor which is known to play a part in inflammatory reactions, and which is connected with oestrogen regulation (Mendoza-Villanueva et al. 2016). Its role in adipogenesis was thoroughly investigated by Hishida et al. (2009), who found proliferation induction of growth-arrested differentiated adipocytes. It also regulates lymph angiogenesis in a process dependent on hypoxia-inducible factor 1-α (Min et al. 2011).

KLF4 is needed for the development of the skin barrier function, and is involved in the regulation of lipid exchange and adipogenesis. More recent works have found a connection between KLF4 and macrophage polarisation (Coppo et al. 2016; Liao et al. 2018), a factor that regulates adipose tissue exchange (Thomas and Apovian 2017).

No significant alterations in gene expression, associated with inflammation, were found in stem cells obtained from lipoedema patients or in differentiated adipocytes (Al-Ghadban et al. 2020).

Ishaq et al. (2021) found significant differences in gene expression and in the lipids and metabolites profiles of tissues, adipose tissue stem cells and adipocytes taken from lipoedema patients as compared with the unaffected controls. Functional assays showed that disturbance of the Bub1-signal transfer drives stronger proliferation of stem cells produced by adipose tissue in cases of lipoedema, indicating a possible mechanism for augmented adipogenesis in such cases. Bub1 codes for a cell cycle regulator which plays a central role in the kinetochore complex, and regulates several histone proteins involved in cell proliferation.

1.6 Hormonal Influences

Lipoedema affects women almost exclusively. The first manifestation, or an increase in symptoms, almost always occurs in phases of hormonal changes (Szél et al. 2014). During puberty, after pregnancies and during perimenopause, the occurrence of anovulatory cycles and absent or weak formation of *corpora lutea* – and thus progesterone – lead to physiological oestradiol dominance; moreover, these phases, and indeed pregnancy, are marked by physiological insulin resistance (Hoyt and Falconi 2015). There is a lack of robust data for the hormonal status of lipoedema patients or a possible link with hormone supply.

There are indications of connections with steroid hormones, including oestrogens/oestradiol, (Child et al. 2010); with the relationship between these and gestagens, such as progesterone; and/or with the distribution and function of their receptors (Kalkhoff 1982; Lindberg et al. 1990; Mauvais-Jarvis et al. 2013). These connections could influence both the increased volume of the subcutaneous adipose tissues and sensitivity to pain.

Idiopathic oedema or fluid retention syndrome, which must not be confused with lipoedema, may appear coincidentally with lipoedema, aggravating the symptoms (Pereira de Godoy and Guerreiro Godoy 2022; Pereira de Godoy et al. 2017). These patients may suffer generalised, symmetrical congestion and swelling, which increase during the course of the day, in the feet, hands, breasts, abdomen and face. In addition to increased capillary permeability, a connection is observed with disorder of the hypothalamic-pituitary-gonadal axis or with oestrogen dominance (Young et al. 1983). The water load test (Streeten 1997) is not effective for differential diagnosis, since it can produce a positive result in cases of both idiopathic oedema and lipoedema.

The following remarks represent subjects of research which so far have not been explored specifically in lipoedema patients.

Oestrogens promote the typical feminine subcutaneous fat distribution by increasing insulin secretion and sensitivity in the target tissue; the adipose tissue of the hips and thighs is particularly oestrogen-sensitive (Lindberg et al. 1990). Depending on the target tissue, they may slow fatty acid oxidation (Kalkhoff 1982; Mauvais-Jarvis et al. 2013), such that adipogenesis may be strengthened locally, even in patients with low systemic insulin levels, while beta oxidation is prevented (Gower et al. 2002). Oestradiol increases the sensitivity of adipose tissues to insulin, so that less insulin is required to prevent lipolysis (Pereira et al. 2015). Conversely, insulin stimulates the aromatisation of testosterone to oestradiol in adipose tissue (Cohen 2001).

In postmenopausal women, oestradiol is formed principally in the subcutaneous adipose tissue (Simpson et al. 1997); in this process, the expression of aromatase mRNA in the buttocks and thighs is higher than in the abdomen, and increases all over the body with age (Bulun and Simpson 1994).

Oestrogens and gestagens have a modulating effect on the psyche, particularly on states of anxiety (Kessler et al. 2005). Both can have an antidepressive effect; however, oestradiol can act as a stimulant and in the absence of equilibrium can promote nervousness and anxiety. Gestagens, in contrast, especially pregnenolone and allopregnanolone, have calming, relaxing, anxiety-reducing effects (Da Pozzo et al. 2012; Quast et al. 2014). Neurosteroids also regulate pain perception: progesterone, and its derivates dihydroprogesterone and allopregnanolone, have a neuroprotective effect on the central and peripheral nervous systems (Joksimovic et al. 2018); an analgesic effect was shown for allopregnanolone in pain modelling (Coronel et al. 2011). The decomposition of progesterone into 20α-OH-progesterone is caused by the aldo-keto reductases (AKR) 1C1, 2 and 3 (Zhang et al. 2009).
The enzyme activity of AKR1C1 makes it a positive regulator of adipogenesis from human adipose tissue stem cells (adipose-derived mesenchymal stromal/stem cells, ASCs) (Liu et al. 2021). A mutation of AKR1C1 was found in a family with monogenic inherited lipoedema, and proposed as the causal gene in this case (Michelini et al. 2020).

Progesterone induces hyperinsulinemia, possibly by a direct effect on the pancreatic islets, and simultaneously promotes glycogen storage in the liver (Kalkhoff 1982). Paradoxically, it enhances the effect of insulin on glucose exchange in the adipose tissue and skeletal musculature. Progesterone stimulates the deposit of body fat, but has catabolic effects on protein exchange (Kalkhoff 1982). Progesterone increases body weight, leading to obesity; it increases the insulin receptor concentration and both basal and insulin-stimulated lipogenesis in the adipose tissue, without reducing insulin sensitivity (Mendes et al. 1985). The lipogenic effect occurs through overregulation of ADD1/SREBP1c (adipocyte determination and differentiation 1/sterol regulatory element-binding protein 1c) at transcription level (Lacasa et al. 2001). Administering progesterone to female laboratory animals leads to an increase in the mass of white adipose tissues in the body and the groin region (Stelmanska et al. 2012). The increase in the blood progesterone concentration was associated with approximately 6-fold and 2-fold increases in the levels of leptin-mRNA and resistin-mRNA respectively, and a halving of the level of adiponectin-mRNA only in the adipose tissue of the groin region. This effect is obviously restricted to the female sex (Stelmanska et al. 2012; Stelmanska and Sucajtys-Szulc 2014). Increased blood progesterone concentration was associated with a significant increase in the expression of lipogenic zymogens in the adipose tissue of the groin in female laboratory animals (Stelmanska and Swierczynski 2013).

The increase in the expression of lipogenic zymogens was associated with an increase in the expression of the sterol regulatory element binding transcription factor 1 (Srebf1) and the S14-gene. Administering progesterone to female laboratory animals led to an increase in feed consumption, body mass and the mass of white adipose tissues. Increasing the blood progesterone concentration led to stronger expression of NPY-genes and reduced expression of CART-genes in the hypothalamus of women subjects (Stelmanska and Sucajtys-Szulc 2014). In male laboratory animals, a high blood progesterone concentration had no effect on feed consumption, body mass or the mass of white adipose tissues, or on the expression of neuropeptide genes in the hypothalamus (Stelmanska and Sucajtys-Szulc 2014).

In a review, Katzer et al. (2021) identified two possibilities for an increase in oestrogen-dependent lipogenesis in lipoedema: altered distribution of the oestrogen receptors of adipocytes (ERα /ERß ratio) with resulting metabolic signals; and/or increased enzyme production for steroid formation by adipocytes, resulting in higher paracrine-controlled oestrogen release. These alterations could lead to an increase in the activation of peroxisome-proliferator-activated receptor (PPAR), the absorption of free fatty acids and glucose by the adipocytes, and angiogenesis; and simultaneously to a reduction in lipolysis, mitochondrial biogenesis and the mitochondrial function. Taken together, these metabolic alterations could lead to increased adipogenesis and so to an increase in the adipose tissues.

Imbalance and / or dysfunction of the steroid hormones can thus, in subjects with a predisposition, be conducive to disordered fat distribution and to increased or diminished pain perception (Bano et al. 2010; Michelini et al. 2020; Xu and Lopez 2018). Furthermore, this situation may lead to a permanently raised cortisol level due to chronic stress, since cortisol, which lowers the pain threshold (Choi et al. 2012), is formed from progesterone under increased demand and so its antagonistic effect to reduce stress and pain is further diminished.

The significance of these findings for explaining the pathogenesis of lipoedema cannot yet be assessed. No studies of lipoedema patients currently exist.

Overweight or obese lipoedema patients present lower mean insulin values than non-lipoedema patients of comparable BMI (Faerber 2018, Nono Nankam et al. 2022). If, however, their increasing obesity leads to the development of insulin resistance, this can cause not only greater lipogenesis and reduced lipolysis, but also increased hunger and higher food consumption (Ludwig and Friedman 2014) (see Ch. 10 Eating Habits).

The average prevalence of hypothyroidism in lipoedema patients (>30% to >40%) is markedly higher than in the general population (2%) (Bauer et al. 2019a; Földi 2009). Steroid hormones also influence the function of the thyroidal hormones: oestradiol negatively, progesterone positively. The influence of the coincident existence of obesity has not yet been described.

1.7 Pain

Pain is described as unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The experience of pain is influenced by biological, psychological and social factors in differing degrees. Pain and nociception comprise different phenomena. These derive not only from the activity of sensory neurons, but it is assumed that, in addition, personal experiences contribute to the concept of pain.

The role of pain is fundamentally adaptive; however, it can have a negative impact on the functions and on the social and psychological well-being of a person. Verbal expression and motor behaviour are the most common of a multitude of possible ways of expressing pain (Raja et al. 2020).

This definition of pain, used by the International Association for the Study of Pain (IASP) in 2020, is based on a multi-dimensional definition (Melzack and Casey 1968). The dimensions of pain include the sensory-discriminatory (intensity, location, quality and duration), the affective-motivating (unpleasantness and the subsequent flight reaction) and the cognitive-appraising (appraisal, cultural values, context and cognitive state). These three dimensions are not independent, but interact mutually. The cognitive state of a person can modulate one or two of these dimensions of the perception of pain (Moayedi and Davis 2013).

Painfulness is the key symptom of lipoedema. Under palpation, pain may appear as superficial and/or subcutaneous. Many clinical observations support a model of slowly developing lipoedema pain. The appearance of symptoms may not be taken seriously, on account of the unobtrusive beginning of lipoedema development during the first few years. During the course of the further dynamic development of the disease, the frequency and severity of the pain may increase. This needs to be confirmed by future scientific studies. The pain caused by lipoedema is not limited to individual dermatomes, but can spread over the whole circumference of the arms or legs (see Ch. 2.2 Diagnosis and Differential diagnosis)

Lipoedema pain has not been sufficiently investigated and characterised in the literature; most authors limit themselves to hypotheses. Hardly any of the available findings appears to be an adequate basis for explaining lipoedema pain. If lipoedema pain is studied from the angle of the pain literature, the mechanism appears to be one of mechanical dynamic allodynia, in which Aβ fibres and probably also C-tactile (CT) fibres are involved. CT fibres can be stimulated principally by manual lymph drainage (MLD), and this might explain the pain-relieving effect of MLD. Conversely, however, this pain-relieving effect of the CT fibres would exclude small fibre neuropathy (SFN) – and therefore probably direct damage to the nerve – as the source of pain (Brenner 2017)

A questionnaire-based study of 592 patients (return rate: 57%) who underwent liposuction during the period 1997 to 2012 showed a postoperative improvement in quality of life in 95% of the respondents, while 97% could dispense completely with further complex decongestive physiotherapy, even 15 years after the operation (Cornely and Gensior 2014).

A recent long-term study of patients after liposuction showed a significant reduction in spontaneous pain and sensitivity to pressure on a 5-point Likert scale 4, 8 and 12 years after the treatment (Baumgartner et al. 2020).

Another recent retrospective study among the clientele of a specialised lymphology clinic in Germany showed that four fifths of the patients with diagnosis of lipoedema presented high psychological stress even before the appearance of lipoedema-associated symptoms (Erbacher and Bertsch 2020). This psychological stress included diagnoses of conditions such as depression, eating disorders or post-traumatic stress disorder, and/or aggravating psychological peculiarities such as burnout syndrome or chronic stress. It must be borne in mind that the majority of the patients in this study suffered coincident obesity, and that the survey was carried out often long after the first appearance of the lipoedema symptoms.

A current study of 20 non-obese lipoedema patients and 20 control subjects matched for Waist-to-Height Ratio (WHtR), all of whom underwent the clinically recognised QST protocol of the German Research Network on Neuropathic Pain (DFNS), shows a different picture (Dinnendahl et al. 2023): the lipoedema patients presented no evident psychometric peculiarities. Lipoedema pain appeared as somatic rather than neuropathic or psychosomatic aversions. All the QST measurements were normal, with two selective exceptions: the pressure pain threshold (PPT) was much reduced and the vibration detection threshold (VDT) was strongly but selectively increased in the affected thigh. On the other hand, the sensory profile on the back of the hand was normal. The authors suggest combining the VDT and PPT values on both the back of the hand and the lateral thigh to give a PVTH score, which offers a very promising potential for diagnosing lipoedema (Specificity: 96.5%).

The measurement instruments used constitute a serious problem with most studies, since the variety of parameters and scales used make comparison very difficult. Furthermore, most questionnaires have not been validated. One exception is a study from 2019, which used the long version of the validated pain questionnaire (DSF) of the Deutsche Schmerzgesellschaft (German Society for Pain) (Gensior and Cornely 2019). Pain was experienced predominantly as either pressing or tugging; overall, “pain” is a multifaceted symptom on which to base diagnosis. The authors show clearly that many questions can only be used with lipoedema patients under certain conditions; as a result, some patients did not complete the whole questionnaire. Some questions, e.g. the correlation of the stages of lipoedema with the suggested alterations in quality of life, could not be answered with the evaluation software used.

To summarise, pain is a multifaceted symptom, hard to pin down and influenced by multiple factors. Finally, the pathogenesis of pain has not yet been explained.

Recommendation 1.2

	Degree of recommendation	Consensus
Considering the divergence in the findings, many aspects and parameters of lipoedema **should** be investigated in greater depth, in order to improve the state of scientific knowledge.	↑	Strong consensus (94.1%)

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2 Definition, Clinical picture, Diagnosis and Differential diagnosis

Tobias Hirsch, Tobias Bertsch

2.1 Definition of the clinical picture

Recommendation 2.1

	Degree of recommendation	Consensus
Pain on pressure or touch, spontaneous pain, and feeling of heaviness **shall** be regarded as symptoms of lipoedema.	↑↑	Strong consensus (100%)

Recommendation 2.2

	Degree of recommendation	Consensus
Disproportional increase in adipose tissue in the limbs without corresponding painful symptoms **shall** not be diagnosed as lipoedema.	↑↑	Strong consensus (100%)

A precondition for a diagnosis of lipoedema is the presence of a disproportional (in comparison with the trunk) increase in adipose tissue, of variable dimensions, in the legs, and less frequently the arms, accompanied by painful symptoms in the region of this disproportional adipose tissue. These symptoms are painful sensations such as pressure pain, spontaneous pain and feeling of heaviness.

An increase in leg circumference that is free of painful symptoms will be referred to as “lipohypertrophy”, the term used habitually in literature (Herpertz 1995; Reich-Schupke et al. 2013), although this concept does not provide an exact histological distinction between hypertrophy and hyperplasia.

2.2 Clinical picture and course of disease

2.2.1 Morphology

The disproportion in lipoedema always presents symmetrically in the legs and/or arms (Cornely 2003; Herpertz 2004). Lipoedema occurs exclusively in the limbs: the trunk, head and neck are not affected. There is no scientific evidence of the development of lipoedema in any other region, before or after liposuction.

The increase in adipose tissue may occur homogeneously in the thighs and/or lower legs and the upper and/or lower arms, or only the lower limbs may be affected. The feet and hands are not affected. Typically, the increase in size shows a marked step from the neighbouring healthy region (“cuff-like” appearance). Painful symmetrical increases of the subcutaneous adipose tissues above and/or below the knee, in the triceps region of the arm and in the lower arm are characteristic of lipoedema. The morphological picture does not support any conclusions on the subjective symptoms.

Typical morphological expressions are given in Table 1 . No recommendation can be made among the numerical systems used for classifying the affected regions due to divergences in the data from the different sources.

Table 1: Location and Categorisation of the affected Regions

Region		According to Herpertz (1995)	According to Schrader (2019)	According to Beltran and Herbst (2017)	According to (Kruppa et al. 2020)
Leg	lipoedema of the buttocks/hips		Type 1	Type I	Type I
	lipoedema down to the knees	Thigh type	Type 2	Type II	Type II
	lipoedema down to the lower legs	Lower leg type			
	lipoedema down to the ankles	Ankle type	Type 3	Type III	Type III
	lipoedema only in the lower leg				Type V
Arm	lipoedema in the shoulders	Upper arm type	Type 4	Type IV	Type IV
	lipoedema down to the Upper arms				
	lipoedema down to the lower arms	Lower arm type			
"Central"	lipoedema in arms and legs	Upper arm & Thigh type			
	lipoedema in arms and legs, predominantly legs			Type V	

Recommendation 2.3

	Degree of recommendation	Consensus
The morphological expression **shall** be descriptive in character, and **shall** not be understood as a classification of severity.	↑↑	Strong consensus (100%)

Recommendation 2.4

	Degree of recommendation	Consensus
The different morphological stages used in the literature to date **shall** not be used as a measure of the severity of the disease. No division into stages based on the painful symptoms has yet been produced.	↑↑	Strong consensus (100%)

Recommendation 2.5

	Degree of recommendation	Consensus
The criterion of "lumpy" adipose tissues, used extensively in the past, **shall** not be used for diagnosis as its validity has not been shown.	↑↑	Strong consensus (100%)

2.2.2 Symptoms

Painful symptoms are felt in the subcutaneous adipose tissue of the affected limbs: pain on pressure, hypersensitivity to touch, feelings of tension and heaviness, spontaneous pain. The intensity of these symptoms is perceived very differently by the women affected.

Subjective perception of swelling of the affected limbs during the course of the day plays a special role in patients' description of the symptoms. In a comparative study of symptomatic lipoedema patients and healthy subjects, it proved impossible to objectivise a perception of swelling during the course of the day, from which the authors concluded that the sensation of increasing circumference must be interpreted as part of the experience of pain (Erbacher et al. 2022).

In the case of a particularly strongly expressed disproportional increase of the subcutaneous adipose tissue in the limbs, complications may develop. These may include static alterations like malalignment of the knee joint (*Genua valga*) and skin infections (intertriginous maceration, skin irritation due to skin-on-skin friction).

In addition to purely somatic symptoms of disproportional adipose tissue distribution and the painful symptoms described above, special attention must be paid to the following coincident conditions in lipoedema patients: overweight and obesity, psychological stress, patient's lack of self-acceptance or acceptance of their bodies.

There are many reports of a propensity to bruising (Forner-Cordero et al. 2021); due to the state of studies, however, this cannot be adduced as a decisive diagnostic criterion (Herpertz 1995; Sucker et al. 2021; Szolnoky et al. 2017; Szolnoky et al. 2008).

The propensity to bruising frequently reported by lipoedema patients could not be objectivised in a comparative clinical study by Erbacher et al. (Erbacher et al. 2023).

Psychological factors may have the effect of either increasing or reducing pain (see also Ch. 8 Psychosocial Therapy).

2.1.1 Overweight and obesity

In addition to their soft tissue symptoms and disproportional fat distribution, a large number of affected women also suffer from obesity, as measured by BMI. Only a minority are within the normal weight bracket (Angst et al. 2021; Bosman 2011; Child et al. 2010; Dudek et al. 2018; Erbacher and Bertsch 2020; Fink et al. 2021). Overweight (BMI ≥ 25 & < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) are the most frequent conditions coincident with lipoedema. Obesity can aggravate lipoedema.

There is insufficient scientific evidence to say that lipoedema is associated with an increased risk of developing obesity.

The body mass index (BMI) is not a robust means of characterising overweight in lipoedema patients, as it leads to false high values in the region of overweight or mild obesity due to the increase in adipose tissue in the limbs. A more accurate assessment of the disproportional fat distribution can be obtained by combining it with the waist to height ratio (WHtR) (Brenner et al. 2023).

Recommendation 2.6

	Degree of recommendation	Consensus
On first documentation and subsequent check-ups, the biometric values of body weight, height, and waist and hip circumference at the least **shall** be recorded.	↑↑	Consensus (94.1%)

Table 2: recommended biometric measurements

Measurement	**Further explanation (as per WHO, 2022)**	**Unit**	**English Term**
Body weight	To one decimal place	[kg]	(body) weight
Height	Measured standing up straight with feet hip-width apart	[cm]	Height
Waist circumference	Measured midway between the curve of the lowest rib and the iliac crest (level with vertebra L3)	[cm]	waist circumference
Hip circumference	Measured at the widest point of the buttocks, keeping the tape-measure parallel with the floor.	[cm]	hip circumference

Recommendation 2.7

	Degree of recommendation	Consensus
Further measurements of the limbs and ratio values **should** be taken at treatment planning and subsequent check-ups depending on which limbs are affected.	↑	Strong consensus (100%)

Table 3: Summary of other measurements

Measurement	**Further explanation** (CEN/TC 205 2009)	**Unit**
Circumference of proximal thigh	5 cm below the midpoint of the crutch with the patient standing upright; point cG in compression stocking measurements	[cm]
Circumference of mid thigh	Circumference in the middle of the thigh, between the midpoint of the crutch and the middle of the patella; point cF in stocking measurements	[cm]
Circumference of proximal calf	Circumference at the narrowest point, just below the tibial tubercle (*Tuberositas tibiae*); point cD in stocking measurements.	[cm]
Maximum calf circumference	Circumference of the calf at its largest point; point cC in stocking measurements.	[cm]

Circumference of the lower calf	Circumference at the proximal end of the Achilles tendon (ca. 5 cm distal of the middle of the calf); point cB[1] in stocking measurements.	[cm]
Circumference of distal calf	Circumference of the ankle at the narrowest point, point cB in stocking measurements.	[cm]

Recommendation 2.8

	Degree of recommendation	Consensus
The lipohypertrophy quotient proposed by Herpertz **can** be used to describe the disproportion.	↔	Strong consensus (100%)

Table 4: calculated measurements

Value	Calculation	Remarks
Body mass index	$BMI = \frac{Body\ weight[kg]}{Height\ [m]^2}$ -n r	Warning: Height in metres!
Waist-to-Height-Ratio	$WHtR\ \frac{Waist\ circumference\ [cm]}{Height\ [cm]}$	
Waist-to-Hip-Ratio	$WHR\ \frac{Waist\ circumference\ [cm]}{Hip\ circumference\ [cm]}$	
Lipohypertrophy quotient	$^{U}PQ = \frac{Circumference\ of\ proximal\ thigh\ [cm]}{Height\ [cm]}$ r	Calculate each side separately.

Table 5: Categorisation of the calculated measurements (Schneider et al. 2010; Stemper 2013; World Health Organization 2000)

		Normal	Overweight	Obesity		
				Class I:	Class II:	Class III:
BMI [kg/m²]		18.5 – 25	25 – 30	30 – 35	35 – 40	> 40
WHtR	15 – 39 years	0.40 – 0.50	0.51 – 0.56	0.57 – 0.68	> 0.68	
	40-49 years	+ 0.01 / year of age				
	from 50 years	0.50 – 0.60	0.61 – 0.66	0.67 – 0.78	> 0.78	
WHR	Female	< 0.8	0. 8 – 0.84	> 0.84		
	Male	< 0.9	0.9 – 0.99	> 0.99		

Recommendation 2.9

	Degree of	Consensus
On first consultation, psychological factors that could play a part in the patient's experience of the disease **should** be recorded.	↑	Consensus (94.1%)

2.1.2 Psychological stress

The data indicate that the psychological health of lipoedema patients is more severely impacted than their physical health (Frambach et al. 2015). The great majority of publications to date have started from the assumption that diagnosis of lipoedema is the cause of this psychological impairment (Dudek

2017; Dudek et al. 2016; Fetzer and Fetzer 2016).

Erbacher, on the other hand, in a population of 150 patients, found that the vast majority of the women were already suffering from psychological stress before the appearance of the typical symptoms of lipoedema (Erbacher and Bertsch 2020). Psychological stress and difficulties with self-acceptance play an important role in the dynamic of lipoedema (see Ch. 8).

2.1.3 Course of Disease

Recommendation 2.10

	Degree of recommendation	Consensus
Lipoedema **shall** not be considered a categorically progressive disease, since progression depends on a variety of factors.	↑↑	Consensus (94.4%)

Recommendation 2.11

	Degree of recommendation	Consensus
The causes of progression of lipoedema **should** be investigated on an individual basis, depending on the patient.	↑	Strong consensus (100%)

Contrary to previous concepts, lipoedema is not considered to be categorically progressive. There is no scientific proof of progression. The first authors to use the concept of progression in this connection were those who originally described the disease, namely *Wold, Allen and Hines* in their 1951 publication. In this publication they already proposed a clear connection between the progression of the disease and increasing weight (Wold et al. 1951).

A recent Spanish investigation of this question strengthens the correlation with weight increase; in two thirds of the patients the disease was stable, while in the remaining third progression was correlated with increasing weight (Forner-Cordero et al. 2021). The volume of the legs only increases with progressive weight gain. Frambach et al. (2016) also described this correlation.

Despite this, it should be stated that the painful symptoms are not correlated with the extent of disproportion or increase of the subcutaneous adipose tissue.

From this it follows that if the patient's weight continues to be stable, the disease is not inevitably progressive, but can remain stable for many years or permanently. In any case there are individual trigger factors that can lead to a progression of lipoedema, apart from weight increase, for example hormonal influences (e.g. perimenopause). These affect not only the expression of adipose tissue increase and disproportion, but also painful symptoms and accompanying psychological factors.

2.2 Diagnosis and Differential Diagnoses

2.2.1 Distinction between Lipoedema and Lymphoedema

Table 6: Differential diagnosis of adipose tissue diseases

	Lipoedema	Lipohypertrophy	Obesity	Lymphoedema
Increase of fat tissue	+++	+++	+++	(+)
Disproportion of the limbs as compared to the trunk	+++	+++	(+)	+
Oedema	ø	ø	(+)	+++
Pressure pain	+++	ø	ø	ø
Symmetry	+	+	+	ø

Recommendation 2.12

	Degree of recommendation	Consensus
Lipoedema **shall** be diagnosed clinically.	↑↑	Strong consensus (100%)

The background to this is the absence of indicative technical or chemical laboratory procedures to confirm a diagnosis of lipoedema.

2.2.2 Appraisal of diagnostic methods and differential diagnoses

Recommendation 2.13

	Degree of recommendation	Consensus
Technical investigative methods **can** be used for differential diagnosis.	↔	Strong consensus (100%)

Distinction of lipoedema from diseases like CVI, obesity and lymphoedema, as well as non-pathological lipohypertrophy of the limbs, by clinical examination and investigating the patient's personal and family medical history can be difficult at times.

Only a small quantity of data, with low power of evidence, is available to support imaging and chemical laboratory procedures. A number of investigations have been published in recent years which use ultrasound diagnosis, MR angiography, scintigraphy or indocyanine green lymphography.

2.2.3 Ultrasound diagnosis

Recommendation 2.14

	Degree of	Consensus

Ultrasound diagnosis **can** be used to exclude for example a phlebological cause for an oedema.	↔	Strong consensus (100%)

Recommendation 2.15

	Degree of recommendation	Consensus
Conclusions on the aetiology of a subcutaneous oedema **shall** not be drawn from B-scan ultrasonography of the oedema.	↑↑	Strong consensus (100%)

In the context of lipoedema diagnosis, duplex ultrasonography is only meaningful for identifying vascular differential diagnoses and co-morbidities like varicose veins, post-thrombotic syndromes, or compression syndromes.

While duplex ultrasonography provides very accurate information on vascular functioning, B-scan ultrasonography serves to distinguish solid from liquid tissue structures. Blood vessels, fluid-filled cysts and bursitis can be identified by the absence of internal echoes. Oedemas are therefore seen as three-dimensional, echo-free, dark areas of tissue (Marshall and Schwahn-Schreiber 2008). Aetiological categorisation of oedemas from ultrasound images is impossible (Becker et al. 2015).

Naouri et al. (2010) compared the echogenicity and thickness of the cutis and subcutaneous layer in patients with lipoedema, patients with lymphoedema and a healthy control group. While a lymphoedema could be distinguished from a thickened cutis by its lower echogenicity, lipoedema could not be safely distinguished from the tissue of the healthy control group.

Hirsch et al. (2018) found an analogous result to that of Naouri et al. (2010), namely that it is impossible to distinguish between the cutaneous and subcutaneous ultrasound scan of lipoedema and normal controls, nor between lipoedema and lipohypertrophy or obesity. Both groups of authors stressed that it was impossible to identify an oedema component in the subject group with lipoedema using high-resolution ultrasound (Hirsch et al. 2018).

The same findings were confirmed by Iker et al. (2019). These authors further established, by the use of additional analytical software, that the subcutis in the lipoedema group was not only thicker than that of the comparison group, but that its echogenicity was significantly lower than in the lymphoedema group and the healthy control group. Limitations of this investigation were the small number of cases and the lack of an obese control group or a control group with asymptomatic lipohypertrophy (Iker et al. 2019).

Kasseroller and Brenner (2019) found diminished compressibility in the ultrasound measurement of the thickness of the subcutis in a small cohort (n = 69) of patients with lipoedema compared with healthy controls. The control groups consisted of patients without lipoedema (n = 12) and men (n = 7) (Kasseroller and Brenner 2019).

Overall, it is clear that definite sonomorphological criteria for the echogenicity of the subcutis in lipoedema patients and reliable cut-off values for compressibility are not currently available. Sonographic criteria indicating the presence of an oedema are not met in cases of lipoedema.

2.2.4 Computed tomography / Magnetic resonance tomography

No specific proof of lipoedema can be obtained by computed tomography (Monnin-Delhom et al. 2002)

The purpose of magnetic resonance tomography and MR lymphangiography is to show and/or quantify liquid content in the tissues/interstitium. Various investigations have been published which deal with the morphology of lipoedema and so-called “lipo-lymphoedema”. Cellina et al. (2020) used MR to investigate increased subcutaneous adipose tissues with homogeneous texture, but found that this procedure showed no oedema in patients with pure lipoedema. It did show dilated peripheral lymph vessels in patients with lipoedema and concurrent lymphoedema (Cellina et al. 2020). Limitations of this study were that exclusively overweight subjects were included (BMI > 31 kg/m²), and the subjects were not assessed phlebologically, so the findings allow no conclusions as to whether those with so-called “lipo-lymphoedema” in fact suffered an obesity-associated accompanying oedema (lymphoedema, venous oedema).

Lohrmann et al. (2009) carried out MR lymphangiography on patients with lipoedema and “lipo-lymphoedema” (n = 13). In the group of subjects with "lipo-lymphoedema" they show broadening of the lymph vessels to > 3 mm, while in subjects with pure lipoedema diameters of up to only 2 mm were measured. They judged that these alterations in diameter were indications of incipient lymphostatic decompensation in lipoedema cases. The nature of so-called “lipo-lymphoedema” is not closely defined in the investigation, so it is likewise unclear whether it there is lipoedema with the additional presence of lymphoedema, or obesity-conditioned lymphoedema (Lohrmann et al. 2009).

Crescenzi et al. (2020; 2018) performed comparative investigations in Stage I and II lipoedema patients (n = 10) with a control group (matched by BMI and lower leg circumference) and obese subjects. They showed that women with lipoedema have a higher sodium content and a higher fat:water ratio in the skin and subcutaneous adipose tissue. The diagnostic potential of this study is restricted by the small number of cases included and other limitations in the study design. Because of the limited dimensions of the MR equipment, subjects with massive lipoedema components and members of the control group with severe obesity could not be included. The individual subjects also presented a wide variety of prior treatments, ranging from complex decongestive physiotherapy through liposuction to operations to reduce stomach size (Crescenzi et al. 2020; Crescenzi et al. 2018).

2.2.5 Indirect Functional Lymphoscintigraphy:

One study using lymphoscintigraphy came to the conclusion that in lipoedema – in contrast to lymphoedema – the rate of lymph transport may be higher in the initial stages, and then decline disproportionately with age in comparison with healthy subjects (Brauer 2000; Brauer and Brauer 2005). These investigations were not matched for BMI.

No systematic investigations of differential diagnosis of lipoedema by lymph scintigraphy are available. Forner-Cordero et al. (2018) investigated lipoedema patients using lymphoscintigraphy and showed that alterations of the radionuclide pattern are also apparent in lipoedema patients.

However, there was no correlation with the severity of the lipoedema symptoms. This study suffers from some limitations. Firstly, there was no clear distinction between lipoedema and lymphoedema patients. Furthermore, the subjects were women aged up to 80 years. Forner-Cordero et al. confirmed that even in healthy people the lymphatic function declines with increasing age (Forner-Cordero et al. 2018). A decisive factor is the age-related loss of glycocalyx combined with increased production of pro-inflammatory cytokines, which increase the permeability of the lymph vessels (Shang et al. 2019).

2.2.6 Indocyanine green-lymphography (ICG-L) and Near-infrared Fluorescence Lymphatic Imaging (NIRF-LI) in lipoedema diagnosis

For newer diagnostic methods like ICG-L and NIRF-LI, only few data are available from small cohorts of lipoedema patients. To date, these methods make no contribution to obtaining a safer diagnosis of lipoedema. The results of the existing studies lead to the conclusion that lymphatic flow disorders do not arise with lipoedema (Buso et al. 2022; Rasmussen et al. 2022).

The absence of lymphatic insufficiency in lipoedema patients is also confirmed in a current paper of the ALERT group of Macquarie University, Sydney. Of 40 patients diagnosed with lipoedema examined by ICG, only two presented lymphatic insufficiency (dermal back flow). One of these two patients was already known to have primary lymphoedema, the other suffered from Grade 2 obesity; the authors therefore assume an obesity-related oedema component (Mackie et al. 2023).

In their paper, the Australian authors also discuss occasional ICG findings of dilatation of the lymph vessels described for patients with lipoedema. The spatial resolution of ICG-L deteriorates rapidly under the skin, leading to distortion of the geometry of the lymph vessels. Although lymph vessels lying deep in the surrounding adipose tissue may appear broadened, these should not be regarded as abnormally extended, since this is attributable to a known optical dispersion property of ICG-lymphography (Mackie et al. 2023; Weiler et al. 2012).

2.2.7 Chemical Laboratory Methods

Recommendation 2.16

	Degree of recommendation	Consensus
Laboratory parameters **can** be used to exclude differential diagnoses, but not to confirm lipoedema.	↔	Strong consensus (94.4%)

There are currently no chemical laboratory methods for identifying lipoedema or distinguishing the condition by differential diagnosis. In the context of oedema diagnosis, routine laboratory measurement of internal parameters could support differential diagnosis only to exclude hypothyroidism, nephrotic syndrome or decompensated cardiac insufficiency as the underlying or accompanying disease. Available parameters include: TSH, FT3, FT4 to exclude hypothyroidism; serum creatinine or GFR and total albumin in the urine to identify kidney function disorder or nephrotic syndrome; and NT-proBP to exclude decompensated cardiac insufficiency.

2.2.8 Alternative Diagnostic Methods

In addition to classic imaging procedures, various other types of equipment have been used in recent years in lymphology and for oedema diagnosis. They are based on measuring the water content of tissues by determining their electrical conductivity (so-called bioimpedance analysis). Available data have not been obtained by evidence-based investigations. A pilot study by Birkballe et al. (2014) using a hand-held equipment for determining the tissue dielectric constant (TDC) showed that some conclusions about the presence of untreated lymphoedema may be drawn using this method, but that it offers no diagnostic criteria for differentiating between decongested lymphoedema, lipoedema and the tissue of healthy subjects. No evaluated data are available to assess the effectiveness of alternative diagnostic procedures like bioimpedance analysis and TDC determination. Published data indicate that they cannot be used to diagnose lipoedema.

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3 Epidemiology

Anya Miller

There are no epidemiological studies which comply with the current diagnosis criteria. Existing data are based on the publications discussed below. Almost all publications cite studies or papers that are over 10 years old.

A frequently cited figure is the estimate of up to 11% from Földi's textbook of 2003. This figure was subsequently withdrawn in a letter to the Süddeutsche Zeitung newspaper on the subject of a news item, and is not mentioned in later editions from 2012 onwards (Berndt et al. 2019; Foldi et al. 2003)

Another frequently cited article was the clinical report of Child et al. (2010). This defines lipoedema as disproportionate fat distribution with more fat below the waist, pressure pain and propensity to bruising. The study subjects were patients of the lymphological clinic in St. George's Hospital, London, between 1994 and 2009. Diagnosis was performed by two specialists; where the diagnosis was positive, other family members were examined. Patients with obesity, or primary or secondary lymphoedema, were excluded. Three hundred and thirty family members were identified from 67 patients. Based on these data, a prevalence of 1:72,000 was presumed. These figures refer exclusively to the selected clientele of this clinic.

A third paper that is frequently cited is by Herpertz; it reports that 15% of the 933 in-patients admitted to a lymphological rehabilitation clinic between May 1995 and March 1996 had lipoedema. The author makes a clear distinction between pain-free adipose tissue increase on the one hand, and symmetrical lipohypertrophy with billowing tissue and pain that he calls lipoedema on the other (Herpertz 1997).

In a sonomorphological investigation carried out in 2008, Marshall and Schwahn-Schreiber reported that 8-17% of all patients in a specialist angiological-phlebological practice were affected by lipoedema, including mild forms (Marshall and Schwahn-Schreiber 2008a). The subjects of this publication were 14 women and one man. Spontaneous and pressure pain were used to distinguish lipoedema from obesity in obese subjects. However, painless lipohyperplasia was classified as an early stage of lipoedema. Two patients were diagnosed in this early stage. The finding for the male subject was described as "similar to lipoedema".

Also in 2008, an article on differential diagnosis of lymphoedema, venous oedema and lipoedema appeared. The diagnostic criteria are cited as a clinical syndrome, after Wienert et al. (2005), characterised by orthostatic leg oedema and an increase of the subcutaneous adipose tissues, concomitant with a fat distribution disorder especially in the thigh and lower leg (Marshall and Schwahn-Schreiber 2008b). The definition suggested by the authors refers to a disorder causing disproportional distribution of the subcutaneous adipose tissues recognizable by sonomorphological alterations, with high fat cell count (lipohyperplasia). They estimate the prevalence in the general population at 8%, following information given in the earlier literature. The findings in 100 patients were analysed to determine non-invasive criteria for diagnosing lymphoedema and lipoedema, and for distinguishing them from venous oedema. No further epidemiological calculations were suggested. The authors state that the figures were estimated values from a selected corpus of patients at a single centre.

In a further study in 2011, the same two authors undertook the definition for the DGP's guidelines (Wienert et al. 2005), based on symmetrical increase of subcutaneous adipose tissue, tendency to orthostatic oedema, propensity to bruising and sensitivity to touch (Marshall and Schwahn-Schreiber

2011).

They recommended division into an early stage with painless lipoedema and a late stage with painful lipoedema. 39% of the 62 women examined had lipoedema according to these criteria; however, the sample included patients with pure *lipomatosis regionalis*. Later stages were defined by the increase in adipose tissue; the reported prevalence was 9.7%.

Fife et al. (2010) described lipoedema as a diet-resistant pathological fat distribution, principally below the waist. In the early stage, only the retromalleolar region may be filled. Further symptoms are propensity to bruising and pain (painful dysaesthesia). In the authors' clinical practice, out of 792 patients with lymphoedema in the lower limbs, 22.7% also presented localised fat increase in the legs. In these cases, they diagnosed concurrent lipoedema. No further epidemiological information was reported.

A single-centre epidemiological investigation with the diagnosis criteria of disproportional fat distribution, pain, propensity to bruising and oedema that increases over the course of the day was published by Rapprich (Rapprich et al. 2015). Investigations of 815 patients in a family doctor's practice, who attended between July 2011 and July 2012 for a wide variety of diseases, resulted in a diagnosis of lipoedema in 5% of cases. Of 126 patients who attended for leg pains, 32.5% were diagnosed with lipoedema.

Forner-Cordero et al. (2012) reported that in a retrospective analysis 18.8% of their patients between 2005 and 2012 had suffered from lipoedema. This was also a single-centre study performed in a hospital setting.

In a further prospective, non-interventional study, data were collected of patients who consulted for suspected lipoedema in a hospital in Spain during the period 2012-2019 (Forner-Cordero et al. 2021). The paper was devoted primarily to the clinical manifestations of lipoedema. No epidemiological data were reported in this single-centre investigation.

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4 Compression therapy for lipoedema

Eberhard Rabe

Recommendation 4.1

	Degree of recommendation	Consensus
In diagnosed cases of lipoedema, compression therapy **shall** be applied for pain relief in the affected limbs.	↑↑	Strong consensus (100%)

Recommendation 4.2

	Degree of recommendation	Consensus
Compression therapy for lipoedema **can** be applied initially with medical compression stockings (MCS), compression bandages (CB) and medical adaptive compression systems (MAC). For long-term treatment, MCS **shall** be preferred in routine cases.	↔ ↑	Strong consensus (100%)

Compression therapy (CT) is considered part of the standard treatment of lipoedema (Rabe et al. 2021). In two surveys in 2014 and 2020, compression therapy was the most common conservative therapy (Lipoedema UK 2014, Paling et al. 2020). CT can be applied with medical compression stockings (MCS), compression bandages (CB) and medical adaptive compression systems (MAC) (Rabe et al. 2021). Furthermore, intermittent pneumatic compression (IPC) can be applied (Rabe et al. 2021). MCS are stocking-shaped knit elastic garments; the effect of CB is achieved by the application of elastic and/or inelastic bandages. In individual cases, the application of CB can lead to constriction, nerve damage or the formation of blisters. Inner padding beneath the CB with cotton-wool or foam bandages and/or *pelottes* prevents these unwanted side effects.

4.1 Mode of action

MCS and PCB have elastic properties, exercising continuous, defined pressure on the limb.

In the first instance, lipoedema is neither an oedema disease nor a clinical picture due to a disorder of the venous or lymphatic functions. The subjective symptoms, and especially the pain, are the focus of attention. Inflammatory processes in the adipose tissue are discussed. The primary object of compression therapy in cases of lipoedema is the reduction of pain and other subjective symptoms. There are no randomised, prospective, comparative studies of inflammation and pain reduction under compression for lipoedema. However, Paling et al. showed in their survey that the painful symptoms diminished under compression therapy in a manner dependent on the frequency of application (Paling et al. 2020). In a current randomised, prospective pilot study, 6 patients with lipoedema were randomised into a group that underwent only an exercise programme, and a second group that had an exercise programme in combination with compression therapy (Compression Class 2, flat knit). The groups were studied over 6 weeks (Czerwińska et al. 2023).

A significant reduction of palpation pain and propensity to bruising was observed in the compression group as compared to the group without compression. Furthermore, in the exercise plus compression group, the circumferences of the legs tended either to stay the same or to be reduced, while without compression they tended to increase. These results indicate that compression therapy in combination with exercise could improve quality of life and reduce painful symptoms.

In venous diseases, it has been shown that pain can be reduced significantly in cases of venous ulcer, and other symptoms can also be reduced (Beidler et al. 2008; Beidler et al. 2009; Moñux et al. 2021; Murphy et al. 2002; Tkaczyk et al. 2021). Beidler et al. also reported reduced inflammation under compression therapy in cases of venous ulcer (Beidler et al. 2008; Beidler et al. 2009). Murphy et al. reported a reduction in serum cytokines in ulcer treatment and compression therapy (Murphy et al. 2002). In lipoedema, the feelings of swelling and heaviness may be generated by the progressive filling of the extensive cutaneous net of blood vessels and the accumulation of fluids in glycosaminoglycans (GAG) over the course of the day. Compression therapy with flat knit materials could counter this filling (Moñux et al. 2021). There are no prospective studies on this question. In addition, compression therapy may shape and model the disproportionate adipose tissue. Reduction of the adipose tissue by compression therapy is not to be expected. Compression therapy has not been proved to provide prophylaxis against progression.

If lipoedema occurs in combination with venous oedema, lymphoedema or hydrostatic oedema, compression therapy may even have a beneficial impact on oedema formation (Rabe et al. 2021).

Recommendation 4.3

	Degree of recommendation	Consensus
Compression therapy **shall** be directed towards the reduction of pain and other subjective symptoms in cases of lipoedema. If lipoedema is combined with oedema of other origins, compression therapy may have a beneficial impact on the oedema formation/reduction.	↑↑	Strong consensus (100%)

Recommendation 4.4

	Degree of recommendation	Consensus
Patients **shall** be informed that compression is not appropriate for reducing adipose tissue.	↑↑	Strong consensus (100%)

The patient's age and the condition of skin, musculature and connecting tissue all play a part in the selection of the compression material, as well as the shape of the arms and legs.

The effectiveness of the compression therapy also depends decisively on the extent to which the compression garment can withstand increasing circumference due to exercise, oedema formation or change from a lying to a standing position, all of which lead to increased pressure beneath the garment.

This property of the compression material is called stiffness (Partsch et al. 2016).

Recommendation 4.5

	Degree of recommendation	Consensus
When selecting and prescribing compression materials, not only the pressure but also the material best suited to the individual **shall** be considered, since the effectiveness of the compression system depends not only on the pressure but also on the properties of the material.	↑↑	Strong consensus (100%)

Because of the occasionally complex leg shapes encountered, with large alterations in circumference over short distances and in some cases associated obesity, there are limits to the suitability of a one-piece MCS; it may be difficult not only to produce, but indeed to put on. In such cases, a combination of several compression elements should be prescribed (e.g. using various elements like Bermudas, leggings and stockings). As lipoedema does not affect the feet or hands, compression leggings or sleeves without gloves can also be considered. Compression therapy must be prescribed by a doctor. In lipoedema, the selection of the best material, the technical requirements for production, the ease with which the system can be put on, and acceptance by the patient all play an important role; close co-operation between the prescribing doctor, the supplier and the patient is therefore recommended.

Recommendation 4.6

	Degree of recommendation	Consensus
To improve adherence to and effectiveness of the compression, the selection of the compression material and/or of a multi-part system **shall** take place in close co-operation between the patient, the prescribing doctor, the therapist and the supplier.	↑↑	Strong consensus (100%)

4.2 Type of knit of the MCS

Medical compression stockings are made in different types of knit (Rabe et al. 2021):

- ***Flat knit with seams, machine-shaped, with at least one knitted thread and one*** inserted elastic thread in every second course. Because of the type of knit, flat knit MCS generally have greater stiffness, but also greater inflexibility, than circular knit MCS. The greater inflexibility allows it to bridge tissue folds better, without slipping in and thus causing constriction. These properties **should** be used for patients with pronounced lipoedema and/or accompanying obesity.
- ***Single and double surface circular knit without seams***, machine-shaped, with at least one knitted thread and one inserted elastic thread in every second course. The stocking can only be adapted to the shape of the leg by altering the size of the loop (tight or loose knit) or the tension of the threads.

  For example, patients with pronounced lipoedema or obesity may present very large

alterations in circumference or deep tissue folds along the arms or legs; for technical reasons these patients cannot be treated with circular knit MCS.

Recommendation 4.7

	Degree of recommendation	Consensus
Lipoedema **can** in principle be treated with either circular or flat knit MCS. As a general rule, flat knit quality **shall** be prescribed for limbs with large changes in the circumference, a conical shape or deep folds of tissue, since circular knit material is not suitable for certain anatomical proportions.	↔ ↑↑	Strong consensus (100%)

Recommendation 4.8

	Degree of recommendation	Consensus
Because of the type of knit, flat knit MCS generally have greater stiffness, but also greater inflexibility. These properties **should** be used in treating patients with lipoedema with or without accompanying obesity. The greater inflexibility allows the material to bridge deeper tissue folds better, without slipping in and thus causing constriction.	↑	Strong consensus (100%)

4.3 Compression pressure

MCS of compression classes (CCL) I, II, III and IV differ in the intensity of the pressure applied to the limb at rest. The CCL are standardised based on the pressure at rest in the ankle area. However, the effectiveness of MCS is affected not only by the pressure at rest but also by the work pressure, and thus the material, which may be of different distensibility and elasticity (stiffness). A higher work pressure can be obtained either by a higher pressure at rest or by higher stiffness. There are therefore MCS of different materials in the different CCL.

Recommendation 4.9

	Degree of recommendation	Consensus
Stocking types and the pressure required, i.e. CCL, **shall** be adapted to the location, the clinical findings and the severity of the painful symptoms and alterations. There **shall not** be a fixed assignment of CCL to the diagnosis lipoedema, since the objective of compression therapy is to	↑↑ ↑↑	Strong consensus (100%)

to improve the subjective symptoms, especially pain.		

Recommendation 4.10

	Degree of recommendation	Consensus
The lowest CCL which will provide sufficient symptom relief **shall** always be preferred. This supports adherence to compression therapy.	↑↑	Consensus (89.5%), Consensus without conflicts of interest (86.7%)

4.4 Side Effects and Risks

Recommendation 4.11

	Degree of recommendation	Consensus
To avoid the side effects and risks of compression therapy, the rules for correct application **shall** be observed. This includes padding of areas at risk from pressure, and regular skin care.	↑↑	Strong consensus (100%)

For Side Effects and Risks the reader is referred to the Guidelines on Medical Compression Therapy of the Limbs with Medical Compression Stockings (MCS), Phlebological Compression Bandages (PCB) and Medical Adaptive Compression Systems (MAC) (Rabe et al. 2021).

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5 Lipoedema and IPC

Stefanie Reich-Schupke

Recommendation 5.1 analogous with IPC Guidelines (Schwahn-Schreiber et al. 2018)

	Strength	Consensus
In treating lipoedema, IPC **should** be used for pain relief and for reducing accompanying oedema of other origins; it can also be applied at home by the patients themselves.	↑	Consensus (94.4%), Consensus without conflicts of interest (94.1%)

There are very few data on the use of intermittent pneumatic compression therapy (IPC) in lipoedema. A Medline search (30.09.2020) with the terms “lipedema” and “IPC” (1) or “pneumatic compression” (10) or “intermittent compression” (7) delivered only a few, overlapping hits. The available data refer exclusively to the use of IPC on the legs.

In everyday clinical practice, IPC is used as a supporting measure in the context of complex decongestive physiotherapy (CDP), but not as a substitute for manual lymph drainage or compression therapy (Fetzer 2016; Herpertz 1997; Mendoza and Amsler 2019; Schwahn-Schreiber et al. 2018). However, it has proved effective in reducing oedema, pain and capillary fragility both in everyday clinical experience and in the context of case series (Svensson et al. 1993; Szolnoky et al. 2008a; Szolnoky et al. 2008b). The device setting must be chosen individually and adapted to the pain experienced by the patient. Multi-stage, multi-chamber thigh length or pants systems have proved effective for treating the legs. Here too, care must be taken to ensure an exact fit.

There is only one prospective randomised pilot study to evaluate CDP in lipoedema therapy; this reports volume reduction in the limb and improvement in painful symptoms in a small number of cases. Additional IPC with empirical device setting produced no further reductions in volume, but it can reduce the costs of manual lymph drainage by reducing the time required, and it is regarded as a safe procedure (Szolnoky et al. 2008a). Szolnoky also reported a reduction in capillary fragility due to CDP and IPC (Szolnoky et al. 2008b; Szolnoky et al. 2011).

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6 Treatment with drugs

Markus Stücker, Gabriele Faerber

Recommendation 6.1

	Degree of recommendation	Consensus
Diuretics **shall** not be used for treating lipoedema. Diuretics may be used for lipoedema patients based on internal indications.	↑↑	Consensus (94.4%)

Lipoedema treatment is essentially aimed at reducing the symptoms, improving functional limitations and preventing progression of the disease (Buso et al. 2019). Treatment with drugs is not considered useful (Gensior and Cornely 2019). This is shown by the fact that it is not mentioned in current review papers (Kruppa et al. 2020), and that no systematically collected data on treatment with drugs are available (Buso et al. 2019). The principal drugs mentioned in reviews are beta-adrenergic agonists, cortico-steroids, flavonoids and selenium, however no detailed suggestions are offered on indication or dosage (Buck and Herbst 2016). Treatment with diuretics is viewed critically. In so-called idiopathic oedema, or fluid retention syndrome, which in around 10% of cases may occur in combination with lipoedema (Pereira de Godoy and Guerreiro Godoy 2022), long-term abuse of diuretics may aggravate or even cause oedema symptoms through counter-regulation. The resulting reduction of the plasma volume may lead to potassium insufficiency, renal salt and water retention, and secondary aldosteronism (Ely et al. 2006; Kuchel and Ethyr 1998; Veluri and Badwal 2019).

Recommendation 6.2

	Degree of recommendation	Consensus
In the initial stages of treatment, or if a particular aggravation of the findings occurs, pain-relieving drugs **can** be considered. In the experience of experts, however, these are not usually effective.	↔	Consensus (88.8%)

Lipoedema pain is an integral element of this disease (Schmeller and Meier-Vollrath 2008).

There are no investigations which demonstrate effective pain-reducing drugs in lipoedema patients. The assumed causes of the pain are inflammation and hypoxia.

Recommendation 6.3

	Degree of recommendation	Consensus
The prescription of drugs associated with weight increases and/or oedema formation **should** be avoided under risk-benefit assessment.	↑	Consensus (88.8%)

In lipoedema patients, weight increase leads to an increase of the adipose tissue of the limbs as well as, in most cases, to an increase in the painful symptoms (Frambach et al. 2016). The drugs referred to in this context would include certain anti-depressants, thiazolidinedione, glitazone (e.g. rosiglitazone).

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7 Physiotherapy of lipoedema

Constance Daubert

7.1 Possible treatments of pain as the lead symptom

Recommendation 7.1

	Degree of recommendation	Consensus
If compression is not applicable in individual cases, or is insufficient to reduce the pain on its own, the lead symptom pain **can** be treated with additional lymph drainage in combination with other therapeutical methods. The objective of manual lymph drainage in these cases is not volume reduction, but modulation of the C-fibres.	↔	Strong consensus (100%)

Recommendation 7.2

	Degree of recommendation	Consensus
Since exercising in compression garments or a training programme is an important element of pain reduction, it **shall** be included in the total therapy concept.	↑↑	Strong consensus (100%)

Recommendation 7.3

	Degree of recommendation	Consensus
A vibration plate **can** be used to raise the pressure pain threshold.	↔	Strong consensus (100%)

7.1.1 Manual lymph drainage

There is no evidence to support the use of manual lymph drainage (MLD) therapy alone in cases of lipoedema. It is investigated as one element in different combinations with other types of therapy. However, it should be mentioned that manual lymph drainage has been shown to have both a sympatholytic effect (Brenke and Seewald 1992; Do et al. 2015; Hutzschenreuter and Ehlers 1986; Kim 2014) and the effect of raising pain tolerance and the pain threshold (Cho et al. 2016; Do et al. 2015; Keser and Esmer 2019; Kim 2014).

According to Schleip (2003), the pressure applied to the abdomen and/or the pelvic region during manual lymph drainage increases vagal activity and may have an anti-inflammatory effect.

In a three-armed intervention study by Antoniak et al. (2022; n = 30), manual lymph drainage in overweight patients resulted in a significant reduction in both the 2h post-load glucose value (2h PG) ($p = 0.050$) and C-reactive protein ($p = 0.041$). In the severely overweight group, the HbA1c level fell significantly after MLD ($p = 0.013$).

This study in overweight patients also found a reduction in insulin values, although without statistical significance.

Since a very low insulin value is sufficient for local lipogenesis in lipoedema patients, this may indicate a possible therapeutic use. However, there is as yet no study of insulin values and lymph drainage in lipoedema patients.

7.1.2 Manual lymph drainage in combination with other therapeutical methods

In a three-armed randomised controlled trial [RCT (n=31)], Atan and Bahar-Ozdemir (2021) showed a greater benefit in the group receiving complex decongestive physiotherapy (CDP) + Exercise programme as compared with groups receiving mechanical intermittent pneumatic compression (IPC) + Exercise programme, and the group which received only the Exercise programme. The significant improvements were found in the areas of pain reduction ($p = 0.045$) and volume reduction ($p = 0.017$ right leg; $p < 0.001$ left leg). The physical functioning sub-score of the SF-36 (QoL) questionnaire also showed significant results ($p = 0.040$). This study included lipoedema patients with Type 3 lipoedema, Stages 3 (30%) and 4 (70% - lipoedema plus lymphoedema).

The CDP of group 1 comprised 30 sessions over six weeks (5 days/week), consisting of lymph drainage, skin care, bandaging for 23 hours and an exercise programme in compression.

Group 2 received 30 sessions of intermittent pneumatic compression (pressure: 50 mmHg) for 30 minutes (6 weeks; 5 days/week).

All groups received the same exercise programme consisting of: Warm-up; flexibility exercises; aerobic training on the treadmill; strength exercises and a cool-down period, totalling 60 minutes.

Szolnoky et al. (2011), in a two-armed RCT with 38 lipoedema patients, showed a significant ($p = 0.0001$) pain reduction (Pain Rating Scale) using CDP. Over five days, the intervention group (n=19) received MLD, IPC, skin care, bandaging and exercise in compression garments. The control group (n=19) received only skin care.

7.1.3 Vibration plate

Schwarze (2012), in a six-week intervention with a total of n = 38 patients, calculated that the use of a vibration plate (Galileo) showed a significantly positive result (increase in pressure pain threshold by 0.70 kg/cm²). In this two-armed RCT (Group 1 Galileo n = 21 / Group 2 leg training n = 17), lasting 12 weeks in total, the participants exercised for 45 minutes twice per week. Group 1 received leg training on the vibration plate for six weeks in the clinic and then six weeks at home; Group 2 received solid leg training for six weeks in the clinic and then six weeks at home. The leg training group (Group 2) also presented a significant increase in the pressure pain threshold, although only after 12 weeks.

Both groups showed no significant alteration of the leg volume.

7.1.4 Aerobic Training, Stretching, Moderate Strength Training

Pain reduction after 12 weeks using leg muscle training was reported by Schwarze (2012). The leg muscle training included ten exercises (aerobic training/strength training) performed 2-3 times/week over 12 weeks. A volume increase was found in the context of the training.

Atan and Bahar-Ozdemir (2021) (see above) also included 60-minute training sessions in their three-armed study. They consisted of a warm-up, stretching, aerobic training on the treadmill, strength-building and a cool-down period. The group which received exclusively the prescribed training finished the trial with significant improvements in pain reduction ($p = 0.002$) and volume reduction (right leg; $p = 0.028$ / left leg; $p = 0.023$). However, when all three groups were compared, the exercise group showed the worst results.

The studies of Volkan-Yazici et al. (2021), Szolnoky et al. (2011) and Szolnoky et al. (2008b) also included an exercise programme in the CDP investigated. The training was not described in detail.

Kronimus et al. (2020) published a pilot study containing the results of three individual cases ($n = 3$). Pain reduction and improved quality of life (SF-36) were found in the course of a 10-week aquatic cycling therapy programme. The patients took part in a 45-minute intervention once per week. The severity of the lipoedema was not described in detail.

Exercising in water provokes increased formation of atrial natriuretic peptide (ANP, Weiß et al. 2003; Wenzel and Muth 2002), which on the one hand promotes renal leachate of water and salt, thus regulating the water in the body, and on the other favours ketone formation (Birkenfeld et al. 2005; Schnizer et al. 2006). According to the research team led by Birkenfeld, ketone formation facilitates lipolysis (Birkenfeld et al. 2005). However, the results of this study show no superiority of exercise programmes compared to other methods of pain reduction.

In this context, Van Esch-Smeenge et al. (2017) already established in 2013 that the strength of the quadriceps femoris muscle is reduced in lipoedema patients ($n = 22$). Moreover, Hodson and Eaton (2013) highlighted misalignment of the hip and/or knee joint in lipoedema syndrome patients in their study. According to the authors, the misalignment is directly connected with hypermobility of the tissue, which is caused by a small number of elastic – and thus retracting – fibres. The misalignment subsequently causes alterations in gait, which in turn can lead to orthopaedic damage, primarily of the hip and knee joint (Volkan-Yazici et al. 2021).

It should also be mentioned, although this has not been reported in any studies in connection with lipoedema, that interleukin-6 (IL-6) is released by exercise, especially after long training sessions (over one hour) (Fischer 2006). IL-6 not only promotes lipolysis but also has an anti-inflammatory effect.

In this context, Krüger (2017) showed in a review that exercising reduces inflammation (MCP-1;TLR 1; TLR 2; TLR4, IL- 10, Il-1RA) in the adipose tissue. According to the author, this is followed by a reduction in systemic inflammation processes as well.

Wegner et al. (2014) showed a continuous decrease of depressive episodes by exercise.

In a study published in 2018, Kandola et al. indicated a reduction in anxiety disorders through physical activity (Kandola et al. 2018).

Various studies have reported a significant improvement in depression through physical activity (Blumenthal et al. 2007; Brosse et al. 2002; Cooney et al. 2013; Dunn et al. 2005; Kvam et al. 2016; Schuch et al. 2016). A review by Eriksson and Gard (2011) considered physical activity to be an effective method of reducing depressive moods (see also Ch. 8).

In a current study by Michalak et al. (2022), a significant correlation ($p<0.01$) was calculated for increased stiffness of the myofascial system with depression. The authors point to the connection between a high level of the TGF-ß 1 cytokine and increased myofascial stiffness. TGF-ß 1 is said to be important in – among other things – stress-caused dysregulation of the vegetative nervous system. A total of 80 people took part in this study: 40 suffered depression and 40 formed the depression-free control group. The stiffness and elasticity of the fasciae were measured by electronic tissue compliance meter (ETCM). Mobilisation of the myofascial system using a foam roll led to an improvement in the depressive status of 69 depressive participants. The authors used the Assessment Memory Bias to evaluate the status of the participants. The participants were randomised into an intervention group (n=38) and a placebo group (n= 31).

7.1.5 Moderate Massage Therapy

According to Field (2014) and Field et al. (2002), moderately intense massage leads to an improvement in the deep sleep phase. This in turn – according to Field – leads to decreased excretion of Substance P and thus to a reduction in pain. The Substance P concentration was measured in the saliva of patients with fibromyalgia.

In other pain syndromes (burns, juvenile rheumatoid arthritis, migraine), saliva and urine tests showed that moderate massage produced a reduction in cortisol levels, together with an increase in serotonins and dopamines (Field et al. 2005; Field et al. 1997; Field et al. 1998; Hernandez-Reif et al. 1998).

There are no comparative studies for lipoedema. A possible transfer of the above findings on the effects of moderate massage therapy should be investigated.

There are international experiments with different massage techniques, which in investigations with small numbers of cases have shown a relieving effect on symptomatic pain (SAT – subcutaneous adipose tissue therapy, Herbst et al. 2017). No recommendation can be derived from these papers.

7.2 Treatments that may be used to treat lipoedema with additional oedema of other origins, with the objective of reducing the oedema

Recommendation 7.4

	Degree of recommendation	Consensus
Complex decompression physiotherapy **should** be used in cases of lipoedema with additional oedema of other origins.	↑	Strong consensus (100%)

Recommendation 7.5

	Degree of recommendation	Consensus
Additional performance of aquatic sports (e.g. aquatic cycling) **can** have a positive impact.	↔	Strong consensus (100%)

7.2.1 CDP plus IPC

In a current study using a Perometer (400 NT) in 14 lipoedema patients (upper limbs affected), Volkan-Yazici and Esmer (2022) showed a significant reduction in the circumference of both arms at three of the four measurement points (p-value of these measurement points < 0.05). Significant results were recorded after daily therapy (5 days/week for 3.5 – 5.5 weeks). The volumes of the arms were also reduced (left p = 0.023; right p = 0.041).

The patients received 45 minutes MLD, 30 minutes IPC, skin care and exercise under compression bandaging. As the hands were not affected, bandaging was applied from the wrists upwards. After the intervention, the patients wore appropriate made-to-measure compression sleeves until the following day.

In a second study, Volkan-Yazici et al. (2021) showed a significant reduction in the leg volume of lipoedema patients (n = 23; p < 0.05) by means of a five to six-week programme of CDP plus IPC. The results of this trial were also measured with a Perometer. According to Murat Esmer (one of the authors), the treatment succeeded with patients of differing lipoedema severity. MLD was performed for 45 minutes, followed by 30 minutes of IPC. The patients were also bandaged.

A study published in 2008 by Szolnoky et al. documented a significant volume reduction (p < 0.05) in 24 participants divided into two randomised groups (Szolnoky et al. 2008a).
The study compared one group (n = 11) treated with CDP (MLD 60 minutes, bandaging, skin care, exercise in compression), with a second group (n = 13) who received an additional ICP treatment (MLD 30 minutes, IPC 30 minutes, bandaging, skin care, exercise in compression).

The addition of IPC to CDP showed no significant benefit.

7.2.2 CDP vs. Aquatic cycling

Becker et al. (2018) investigated the effect of aquatic cycling (AC) in n = 10 lipoedema patients (2 lipoedema, 8 lipoedema with additional lymphoedema) over a period of ten weeks. Five randomised patients formed the control group, with MLD alone (1-2 times/week).

The intervention group received aquatic cycling once per week in addition. No significant volume reduction was found in either group. In the direct comparison between the groups, a volume reduction was found in the intervention group (plus AC) [266.37 ccm (SD 435.60)]. According to Becker et al., the MLD group showed a volume increase [439.95 ccm (SD 1246.90)].

7.2.3 Galileo (Vibration plate) / Leg training

In Schwarze's study described above (Schwarze 2012), neither the group treated with the Galileo vibration nor the leg exercise group showed a volume reduction. On the contrary, the author reported a volume increase – although not significant – in the group treated with leg training but without the vibration plate.

7.3 Lipoedema treatments that may reduce hypertrophic tissue

7.3.1 Shock-wave Therapy (SWT)

Siems et al. (2005) showed an anti-hypertrophic effect from the treatment of 26 lipoedema patients by "shock-wave" therapy (SWT). This was established by the plasma malondialdehyde (MDA) and plasma protein carbonyl concentrations, and compared with the plasma data of 80 unaffected subjects.

The intervention was carried out in two groups, with Group 1 receiving CDP + SWT, and Group 2 only SWT.

Group 1 showed clearer effects. No significance was reported.

7.3.2 Manual Subcutaneous Adipose Tissue Therapy (SAT)

In a study by Herbst et al. (2017), an improvement in the tissue structure, namely an antifibrotic effect, was shown in seven patients.

7.4 Lipoedema treatments that may improve the quality of life (QoL) of lipoedema patients

Recommendation 7.6

	Degree of recommendation	Consensus
Manual lymph drainage in combination with other therapeutic methods **should** be considered to improve the patient's quality of life (QoL).	↑	Consensus (94.4%)

Three studies investigated the effects of therapeutic methods on the quality of life of lipoedema patients (Atan and Bahar-Ozdemir 2021; Donahue et al. 2021; Kronimus et al. 2020). Although carried out with relatively few participants (n = 7 Donahue et al./ n= 3 Kronimus et al.), manual lymph drainage in combination with other therapeutic methods was shown to have a positive effect in lipoedema patients both in Stages 3 and 4 (Atan and Bahar-Ozdemir 2021) and in Stages 1 and 2 (Donahue et al. 2021).

In the study by Kronimus et al. (2020), aquatic cycling was shown to improve quality of life in two out of three cases.

Schleip and Jäger (2014) indicated a correlation between psychosomatic diseases and altered interoceptive signal retransmission in myofascial systems. More recent studies support this assertion (Michalak et al. 2022). According to the authors, interoceptive signal transmission is strengthened significantly by anxiety disorders and depression. There are no studies in lipoedema patients.

7.4.1 Lipoedema treatments that may reduce high sodium levels in lipoedema tissue

Donahue et al. (2021) established a significant reduction of the sodium level ($p = 0.005$) in seven patients, observed by 3 Tesla sodium and water magnetic resonance imaging (MRI). An increase in sodium levels in the tissue of lipoedema patients was postulated by Crescenzi et al. (2018) and Crescenzi et al. (2020).

7.5 Physiotherapeutic Investigative Approaches

7.5.1 Lipoedema treatment that may reduce capillary fragility in the lipoedema

Szolnoky et al. (2008b) showed ($n = 38$) a significant reduction ($p < 0.001$) in capillary fragility by use of CDP plus IPC. The 21 patients in a five-day study received MLD for 30 minutes, IPC for 30 minutes (30 mmHg), bandaging, skin care and exercise in compression (Walking: twice daily for 30 minutes). The control group ($n = 17$) were treated with skin care.

In comparison with another control group ($n = 10$), lipoedema patients presented a significant increase in the number of petechiae ($p < 0.05$)

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8 Psychosocial Treatment

Gabriele Erbacher

8.1 Lipoedema and psychosocial stress

Recommendation 8.1

	Degree of recommendation	Consensus
In diagnosing lipoedema-associated pain, psychosocial factors **shall** be considered in addition to medical factors under the bio-psycho-social concept.	↑↑	Strong consensus (100%)

Recommendation 8.2

	Degree of recommendation	Consensus
Psychological disorders can affect the symptoms and quality of life of lipoedema patients and **shall** be considered in lipoedema diagnosis and treatment. These include for example eating disorders, depression, post-traumatic symptoms after violence and abuse. An interdisciplinary approach shall be used in treating these cases.	↑	Strong consensus (100%)

Women with diagnosis of lipoedema may suffer numerous psychosocial stresses; the overwhelming majority of patients also present pictures of psychological disorders, e.g. depression (Dudek et al. 2016; Dudek et al. 2018; Erbacher and Bertsch 2020; Fetzer 2016; Frambach et al. 2015; Frambach et al. 2016; Schubert and Viethen 2016a; Schubert and Viethen 2016b).

Study results based on validated questionnaires completed by women with lipoedema from different countries show that women with lipoedema suffer significantly higher levels of psychological, emotional and social disorders in comparison with women in the general population (Dudek et al. 2016; Dudek et al. 2018; Romeijn et al. 2018).

The proportion and intensity of psychological disorders can differ considerably depending on the respective outpatient or inpatient setting.

In a one-armed, retrospective, single-centre cohort study in a specialist lymphology clinic with 150 patients, all with confirmed diagnosis of lipoedema, 46.7% of the women presented pain-relevant disorders like mild to moderate depression, anxiety disorders, eating disorders or post-traumatic stress disorders. Furthermore, 33.3% of the women in the study presented psychological abnormalities, such as psychophysical exhaustion syndrome or burnout (Erbacher and Bertsch 2020; Maslach et al. 1997).

The results of the study by Frambach et al. (2015) show that the dimension “psychological health” in women with lipoedema is even more severely affected than the dimension “physical health”, measured with the internationally recognised SF 36 quality of life instrument (Bullinger and Kirchberger 1998).

A cross-sectional study compared the expression of emotion regulation (measured with the Difficulties in Emotion Regulation Scale (DERS)) and the anxiety (measured with the Hamilton Anxiety Rating Scale (HAM-A)) in 26 patients with medically confirmed lipoedema, with those of a healthy control group containing 26 subjects of the same age (Al-Wardat et al. 2022). In the questionnaire, the lipoedema patients showed considerable difficulties in emotion regulation (Scales: impulse control, goal-controlled behaviour, emotional awareness, emotional clarity, non-acceptance of emotional responses and emotion regulation strategies) and a stronger expression of anxiety symptoms than patients without lipoedema. The authors therefore recommend that more attention should be paid to the emotion regulation and psychological status of lipoedema patients.

Previous studies suggest that the psychological stresses and disorders found result from lipoedema, and that the disease is responsible for these psychological symptoms. Current data, based on independent investigation of the two conditions (lipoedema-associated pain and psychosocial stress), followed by establishment of the temporal relation between them, show that in 80% of the patients, psychological stress developed within 12 months before the development of soft tissue pain, and therefore of lipoedema symptoms (Erbacher and Bertsch 2020).

These data therefore hint at lipoedema not being the cause of the psychological symptoms.

A review investigated the influence of the patient's psychological condition on both the development of the initial symptoms of lipoedema and the severity of the pain experienced (Czerwinska et al. 2021). The authors concluded that psychological disorders increase the pain experienced from lipoedema.

8.2 Obesity and psychosocial stress

The great majority of women diagnosed with lipoedema suffer from another disease, obesity. Data from some European centres where lipoedema patients are treated show that according to their BMI up to 80% or more of lipoedema patients suffer from obesity (BMI$\geq$ 30 kg/m^2), and from morbid obesity in around 50% of cases (BMI $\geq$ 40 kg/m^2) (Child et al. 2010; Dudek et al. 2018; Erbacher and Bertsch 2020). Note that the BMI is a problematic measure in lipoedema patients (see Ch. 2). In women with lipoedema, treating obesity is especially important, since coincident obesity is an aggravating factor for lipoedema.

Furthermore, obesity itself is an independent risk factor for the occurrence of psychological disorders (Luppino et al. 2010; Sikorski et al. 2015).

A large random sample of 495 normal weight, 1,550 overweight and 910 obese individuals from the general population and from rehabilitation clinics showed that obese people suffer from psychological disorders like depression, anxiety or somatic symptom disorders significantly more frequently than normal weight individuals (OR 2.0 and 1.4 respectively) (Baumeister and Harter 2007).

Furthermore, the usually coincident co-occurrence of lipoedema and obesity can lead to increasing problems of mobility. According to more recent data, the perceived limitation of mobility implies a clear increase in the risk of developing depression (Linsmayer et al. 2019).

A meta-analysis of prospective studies illustrates the bi-directional dependence between depression and obesity: thus, obesity increases the risk of suffering from depression by 55%; and the presence of depression increases the risk of obesity by 58% (Luppino et al. 2010).

Particularly in the context of the current ideal of beauty defined by slimness and thin legs, the disproportional distribution of the adipose tissue in the legs (and sometimes the arms also) may lead to difficulties in accepting their bodies among many women affected by lipoedema, and to stigmatisation (Dudek 2017; Fetzer 2016; Nath 2019).

Furthermore, the greater the demonstrable media consumption of women and girls, the stronger their dissatisfaction with their own bodies (Swami et al. 2010). The ideal of beauty adopted by young women is already below normal weight for their age group (Schuck et al. 2018). Vulnerable girls and women may suffer social pressure, entering a diet spiral that in turn leads as a rule to further weight increase (Bertsch and Erbacher 2018b; Mann et al. 2007; Pietilainen et al. 2012).

8.3 Psychological stress and chronic pain

A link between psychological stress and the experience of pain has been well described for many "pain diseases" (Baerwald et al. 2019; Bic off et al. 2016; Linsmayer et al. 2019; Tegethoff et al. 2015; Viana et al. 2018).

A chronic physical symptom, such as pain, tiredness or dizziness, that leads to significant functional limitations in important areas of life (work, family, free time), can be diagnosed as a somatic symptom disorder and treated by an interdisciplinary team. For women with lipoedema and limitations in important areas of life, this means that their pain will be taken seriously as the combined effect of physical and psychological factors.

The current state of investigation into the impact of psychological factors on the experience of pain and the risk of the disease becoming chronic is quite consistent. There is scientifically proven evidence that the following factors may lead to a significant increase in pain (analgesic nocebo effect) (Briest and Bethge 2017; Chibuzor-Hüls et al. 2020; Klinger 2017; Vlaeyen and Linton 2000; Zale et al. 2013):

- Catastrophising thoughts
- Anxiety (especially disease-related anxiety)
- Passive pain behaviour (pain-sparing behaviour and avoidance of exercise for fear of renewed pain) (Fear Avoidance Model)
- Loss of control
- Depression, helplessness and hopelessness
- Distress (negative stress)
- Attention to pain and
- Expectation that pain will increase
- Violence/sexual abuse (Erbacher and Bertsch 2020; McLaughlin et al. 2016)

For these factors in particular, the information on the disease given to the patient plays an important role (Dudek et al. 2016; Erbacher and Bertsch 2020).

The results of incorrect information may not only lead to an increase in catastrophising thoughts (e.g. fear of progression of the disease) (Bertsch and Erbacher 2018a), but also harm the doctor-patient relationship (Mendoza 2020).

The experience of physical violence and/or sexual abuse also plays an important role in lipoedema. In a study of 150 patients with confirmed diagnosis of lipoedema, 52% reported this background (Erbacher and Bertsch 2020). The patients also presented links between psychological disorders like depression or post-traumatic stress disorders, and the perceived maximum and minimum severity of pain in everyday life (Erbacher and Bertsch 2020). 52% reported experiencing physical violence or sexual abuse in the past, which is clearly higher than the occurrence in the general population (Erbacher and Bertsch 2020).

A prospective study confirmed this aspect also for other types of chronic pain: childhood violence, leading to psychological disorder, is a predictor of painful conditions in the future (McLaughlin et al. 2016). A decisive factor is excessive pressure to get over the experience, rather than the actual event.

In addition to the above-mentioned pain-modulating factors, chronic stress plays a central role in pain perception. Due to the strong overlap between the neurobiological systems for managing stress and pain, pain may be generated centrally. This is called Stress-induced Hyperalgesia (SIH) (Egloff et al. 2016).

8.4 Patient education and psychosocial therapeutic approaches

The pain-strengthening factors presented in Ch. 8.3 enable us to derive the factors that could lead to pain relief (Klinger 2017):

- De-catastrophising
- Reducing fear of pain from exercising
- Giving the patient means of control and certainty with respect to the pain and its course
- Treatment of (pain-associated) depression
- Focusing the attention away from pain to other aspects of existence that can enhance the quality of life
- Expectation of pain relief

Investigation has shown that dismantling catastrophising thoughts and constructing encouraging ones is an important factor in handling pain, and moreover leads to long-term stability in the outcome of therapy (Christiansen et al. 2015).

Approaches that may be helpful for women with lipoedema are: Pain Neuroscience Education (Louw et al. 2016; Moseley and Butler 2015a; Moseley and Butler 2015b), Cognitive Behavioural Therapy CBT (Probst et al. 2019), Acceptance and Commitment Therapy (Sturgeon 2014) and EMDR (Gerhardt et al. 2016).

While the object of Cognitive Behaviour Therapy is to break out of the vicious circle of fear avoidance (Liedl and Knaevelsrud 2008), Acceptance and Commitment Therapy, based on mindfulness, can increase psychological flexibility. Both therapeutic approaches show a positive influence on pain intensity and an improvement in depression and quality of life (Hughes et al. 2017; Veehof et al. 2016).

The factors described above, which contribute to pain relief, should be incorporated into approaches which combine patient education and the encouragement of self-management (c.f. Ch. 9). The provision of evidence-based information and the fostering of realistic expectations as to possible improvement in the symptoms are of the essence.

To ensure “Good Psychotherapy” (Gerger et al. 2020), it is important to involve the patient in decision-making processes and to encourage her to take an active role, enabling her to contribute to the improvement in her quality of life.

8.5 Screening for important and frequent psychological stress, as per the recommendations of other Guidelines

Recommendations for screening are given in the appendix.

Recommendation 8.3

	Degree of recommendation	Consensus
Aggravating psychological diseases (e.g. severe eating disorder or severe depression) **shall** be treated before any operation is carried out.	↑↑	Consensus (94.4%)

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9 Self-management

Gabriele Erbacher, Susanne Helmbrecht

Recommendation 9.1

	Degree of recommendation	Consensus
Effective self-management is an important component of health literacy. It **shall** be fostered, and the patient encouraged to take an active role. Problem-solving strategies and concrete individual therapy targets **shall** be developed jointly, to further increased self-efficacy.	↑↑ ↑↑	Consensus (88.8%)

Recommendation 9.2

	Degree of recommendation	Consensus
Self-management **shall** be supported by appropriate measures on the part of the treatment team, but the responsibility remains with the patient. The treatment team **should** provide positive encouragement for achievements. Confrontational behaviour **shall** be avoided.	↑ ↑ ↑↑	Consensus (88.8%)

9.1 Definition of self-management and differentiation from similar concepts

According to Seidel et al., self-management is defined as the ability of affected people to take control of their own life and its development. It includes contributory competences like motivation, target-setting, planning, time management, organisation, controls for success, and feedback (Seidel et al. 2019).

People with a chronic illness should be enabled to live with it effectively. This includes setting their own targets and the ability to communicate well with relations and friends about the disease and their targets and needs (Dierks 2019).

Self-management is to be distinguished from similar concepts like Health Literacy and Empowerment. While self-management is a concept focused on the individual for overcoming (Dierks 2018), political empowerment is a concept focused on involvement, enablement and change.

Originally, information transmission in health care was mainly carried out in an instructive or educational manner, and self-management was excluded. The basic assumption underlying this approach was that only the provision of disease-specific information by an expert would lead directly to a behavioural change, which in turn would achieve an improvement in the clinical outcome. However, this proved to be an over-simplified approach. Several reviews of randomised controlled studies confirm that merely passing on relevant information to the patient – without incorporating self-management strategies – is not very effective (Gibson et al. 2002; Norris et al. 2001).

According to modern knowledge, patient education grounded on evidence-based information and self-management go hand in hand.

The provision of scientifically based information about the disease in the framework of patient education is essential in cases of lipoedema. Successful self-management must be built on the basis of valid information. False information obstructs successful self-management and can lead to an aggravation of the course of the disease (Mendoza 2020).

Current self-management approaches assume that the provision of problem-solving strategies for living with the disease and increasing self-efficacy (confidence in one's ability to overcome challenges by one's own actions) is central to achieving a clinically significant long-term improvement (Bodenheimer et al. 2002).

In cases of lipoedema this could mean that if patient education and self-management go hand in hand, it is the lipoedema patient herself – after the treatment team – who has the greatest impact on the success of treatment.

9.2 Fostering self-management

Self-management can be fostered from two angles: first by measures applied directly to the patient (e.g. self-management courses); and second by supportive appraisals on the part of the treatment team (doctors, therapists of various professional groups).

The treatment team can foster self-management by the following measures:

1. Building up a relationship and gaining the patient's confidence
2. Listening, and offering positive appraisal to strengthen the patient's capabilities
3. Discussing positive and negative influences, praising effort
4. Supporting the patient with concrete techniques:
   Open questions, deliberation, appreciation, summaries, providing information (ask permission, give information, enquire subsequently).
5. Providing or recommending informative brochures, web-sites, magazines to read at home.

It must first be established how capable the patient is of self-management. In the event that her ability is limited, ask about and organise support by other people: e.g. does she have a partner, family, self-help group or network that can give support?

Many people – particularly among lipoedema patients (Erbacher and Bertsch 2020) – have only a limited capability for self-management due to psychological disorders such as depression (Egede 2005; Reinecker and Siegl 2004). Implementing self-management is then clearly hindered, to some extent, by the psychological disorder, and this must not be confused with lack of will-power or motivation. These patients need close and detailed support through the different phases of the disease, or should be referred to other professional groups such as psychotherapists.

Self-management by the patient herself can be fostered by the following measures:

1. Training in problem-solving strategies (Defining the relevant problems, obtaining relevant information, weighing up different possible solutions, deciding on the solution to apply, application and evaluation, assessing the outcome)
2. Learning to take decisions (application of the knowledge acquired to everyday situations)
3. Increasing self-efficacy (knowing, and knowing how to use, one's own resources)

In the framework of rehabilitation, include the following modules in the training module to foster self-management in medical rehabilitation (SelMa) (Meng et al. 2019):

1. Target setting (What am I undertaking? What would I like to change at home?)
2. Planning (How can I do it, in concrete terms?)
3. Overcoming obstacles, (What could go wrong? What could I do then? How do I know if I have succeeded?)
4. Examining and rewarding.

Special self-management programmes can support successful self-management by patients with chronic diseases. Health experts foster self-management by behaviour-oriented advice and motivating talks given on a person-to-person basis (Miller and Rollnick 2015). The target should be for the patient to become the expert on her own disease.

The patient's first task is to adapt her everyday life to the demands of her disease, adopting a new lifestyle. Forming new, healthy habits takes between 18 and 254 days, and the challenge involved should not be underestimated (Lally et al. 2010).

The so-called 5As strategy for patient-centred counselling can be used as a kind of introduction to self-management.

The critical component of any intervention for fostering self-management in health is a co-operative relationship between health experts (doctors and therapists) and patients.

In the 5As strategy for patient-centred counselling, which has already been successfully applied in obesity counselling, the treatment team pays attention not only to the patient's psychological situation, but also, and above all, to her motivation (Vallis et al. 2013). The counselling is divided into five steps:

Ask, **Assess** (Considering expectations, behaviour and progress), **Advise**, **Agree**, **Assist**

Interventions to foster self-management are aimed basically at behavioural changes. Maintaining the new behaviour patterns depends on the lipoedema patient´s motivation and confidence in her own capabilities.

Behavioural changes for the self-management approach only succeed if the patient has strong grounds for changing her condition. She must therefore see that the benefits of such changes clearly outweigh the objections. The probability of success is higher if she sets her own targets (Dolatschek 2002).

Supportive appraisals on the part of the treatment team can increase the patient's motivation and ability to achieve an active role as the expert on her disease. The willingness of women with lipoedema to assume this expert role is often manifested in their participation in self-help groups or websites. Motivation and self-confidence are the principal foundations of behavioural changes.

They can be enhanced by well targeted questions where the patient has poor self-efficacy or sets herself low health targets.

If a patient sets herself a low target in a matter of great importance for her health, therapists often react with reproaches.

People are much more likely to alter any of their dearly-held habits if they convince themselves, than if they feel that they have their backs to the wall defending their burdens or bad habits. Leaving old habits is more difficult than learning new ones.

Research results confirm the long-term effectiveness of motivational interviews (Lundahl and Burke 2009).

On the other hand, patients often fail through placing excessive demands on themselves (Miller and Rollnick 2015).

Unhealthy patterns of behaviour (such as binge-eating as a response to stress) play a neurobiological role in regulating stress. The stress level is reduced in the short term, which the brain recognises as a reward.

9.3 Self-Management Programmes and their Effectiveness

In patients with chronic diseases, good self-management leads to improvements in their health, their everyday functionality and their quality of life (Franek 2013).

Fostering self-management (e.g. in self-help groups or groups led by a professional) could be directed towards generally effective programmes for fostering self-management.

The effectiveness of self-management has been investigated and confirmed for various chronic diseases in a large number of proposals (Taylor et al. 2014).

Critical voices question the rather unspecific competences included in these proposals, and demand the creation of programmes that are more clearly and specifically designed to address the problems with overcoming any chronic disease, since research findings raise the suspicion that concentrating exclusively on problem-solving competences and the range of skills required for these is insufficient (Haslbeck and Schaeffer 2007)

So far, hardly any specific proposals have been published for lipoedema.

One approach is the lymph self-help self-management programme published in 2009. This was appraised in 2018/2019 through the subjective evaluations of the participants. On conclusion of the workshop, they reported that they felt better informed and subjectively better enabled to live with the disease.

9.3.1 The INSEA Initiative for Self-Management and Active Living

INSEA stands for “Initiative for Self-Management and Active Living” and was developed to foster self-management by people with a chronic disease. It is evidence-based (based on subjective evaluation and reporting by participants) and licensed.

Part of the concept is to train sufferers of very different diseases together: there is no specific content referring to lipoedema.

9.3.2 Lipoedema Self-Management Programme

The “Healthy and active living with lipoedema and lymphoedema” (GALLiLy) self-management programme, promoted by AOK, is aimed at patients with lipoedema and/or lymphoedema (Helmbrecht and Kraus 2021). The self-management components are similar to those of the INSEA programme, however the medical contents are specially adapted for lipoedema. An evaluation of the GALLiLy course carried out in 2018-2019, like the evaluation of the INSEA programme, focused on the participants’ satisfaction with the training programme. Reporting by the participants was mainly positive in this respect. 85% of the participants (n = 122, of whom 21 were diagnosed with lipoedema and 55 with “lipoedema and lymphoedema”) felt that they were subjectively better prepared for self-management (Helmbrecht and Kraus 2021). Data were recorded at the time and are now being evaluated to assess the medium to long-term effectiveness (as at December 2022).

To date there are few proposals directed especially at women with a diagnosis of lipoedema. Most proposals are aimed at both lymphoedema and lipoedema patients.

Self-management training for lipoedema patients should include the following elements:

- Stress management
- Physical activity, ideally sport, where possible in compression, to reduce painful symptoms
- Improving fitness by progressive increases in physical demand
- Avoiding overweight, weight stabilisation; dieting should be avoided due to the tendency for patients to abandon diets. Where applicable, additional reliance on medical support
- Compression as an additional basic element of treatment, including understanding – where compression is appropriate – the importance of using compression on a daily basis: information as to the right compression class, and where appropriate a multi-part system, instruction on and help with donning the compression system by the provider, donning aids.
- Information on rectification of a compression garment that does not fit. Pain must not be tolerated.
- Possibility of involving the patient’s partner or contracting a nursing service
- Self-bandaging, if the stocking system is insufficient or not (yet) ready
- Exercising in compression: aquatic exercise is particularly effective; activating muscle and joint pumps
- Skin care, since compression exercises great stress on the skin, including: healthy, clean skin and application of creams; enriched cream appropriate to the skin type
- Plan active pauses

- Self-treatment, including exercises to increase mobility, circles with the shoulders, breathing therapy/breathing exercises
- The patient remains responsible for her treatment: however, support from others is to be recommended
- Suggest possible occasions for support, e.g. when ordering new compression stockings, in weight management, seek support in the patient's environment, e.g. a supportive partner, family or network, self-help group. If necessary, refer for psychotherapy

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10 Eating Habits and Weight Management

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Recommendation 10.1

	Degree of recommendation	Consensus
The patient **shall** be advised at an early stage of the negative impact of obesity on lipoedema and the significance of healthy eating habits and an active lifestyle.	↑↑	Strong consensus (100%)

Recommendation 10.2

	Degree of recommendation	Consensus
Patients **shall** be made to understand that if they suffer concurrent overweight or obesity, their leg volume can be reduced by weight reduction through an appropriate diet.	↑↑	Strong consensus (100%)

Recommendation 10.3

	Degree of recommendation	Consensus
Nutrition and weight management **shall** be used to help patients maintain or regain mobility and functionality, and prevent the disease from progressing. Goals **shall** therefore be on the one hand achieving or maintaining a healthy body composition, and on the other the reduction of pain and other symptoms.	↑↑ ↑↑	Strong consensus (100%)

Recommendation 10.4

	Degree of recommendation	Consensus
Treatment of overweight and obesity **shall** be included in the overall concept of lipoedema treatment, since both can lead to progression in the volume of the limbs and aggravation of the disease.	↑↑	Strong consensus (100%)

Recommendation 10.5

	Degree of recommendation	Consensus
The basis of weight reduction with coincident obesity **shall** always be a combination of nutritional measures and physical activity, and if appropriate behavioural methods, and include both the weight reduction phase and long-term stabilisation.	↑↑	Strong consensus (100%)

A large proportion of lipoedema patients are overweight or obese. Even though lipoedema is presumed to be genetically determined, occurring basically independent of body weight, the symptoms are nonetheless influenced considerably by lifestyle and eating habits (see Ch. 2). The first appearance or any aggravation of the symptoms generally occurs during a phase of hormonal change (Szél et al. 2014), when weight increases are also frequent. Although a weight increase always leads to an increase in limb volume (Forner-Cordero et al. 2021, Frambach et al. 2016), the painful symptoms do not correlate with the extent of the disproportionate volume increase or increase in the subcutaneous adipose tissue. It may be positively or negatively influenced by a series of other factors, including hormonal alterations, diet, psychological factors and physical activity.

Coincident obesity can certainly lead to reduced mobility and other accompanying diseases, which worsen the overall picture and end in a vicious circle. These may include orthopaedic complications, obesity-associated lymphoedema and cardiovascular diseases.

Reducing overweight and/or treatment of pre-existing obesity to achieve or maintain a healthy body composition are therefore very significant in the overall concept of lipoedema treatment. Weight management is indispensable in cases of severe obesity and obesity-associated diseases.

Either a conservative or a surgical approach may be recommended, depending on the patient's weight situation and wishes; the basic principles of the conservative treatment concept must also be followed after surgery.

Weight reduction must always be based on a combination of nutritional therapy, physical activity, and where appropriate behavioural therapy measures, and include both the weight reduction phase and long-term stabilisation (Centre for Public Health Excellence at Nice and National Collaborating Centre for Primary Care 2006; Ditschuneit et al. 1999; Hauner et al. 2014; Logue 2010; Ross Middleton et al. 2012; Södlerlund et al. 2009).

A sufficiently high quantity of proteins should be provided to ensure that weight reduction occurs by reducing fat mass and not muscle mass; this will enable the patient to reach and maintain a healthy body composition. This is characterised by a balance between fat mass and fat-free mass (FFM), especially body cell mass (BCM), appropriate to the patient's age and sex. Proteins will also prevent any reduction in the patient's energy consumption and/or basal metabolic rate, which are hindrances to sustained weight loss; sarcopenic obesity can be recognised and treated (Claussen et al. 2022; Ebbeling et al. 2012; Faerber 2014; Larsen et al. 2010).

As a large proportion of patients are found to suffer from various eating disorders (Erbacher and Bertsch 2020; Stutz 2013), suspicion of such a condition should be clarified, and nutritional therapy should be carried out with psychological support.

Recommendation 10.6

	Degree of recommendation	Consensus
It **shall** be explained to patients that they should avoid short-term diets, and instead to adapt their eating habits permanently to a healthy, individually tailored nutrition.	↑↑	Strong Consensus (100%)

Many lipoedema patients fear that their disease condemns them to permanent weight increase. This leads on the one hand to numerous unsuccessful attempts to diet and a high incidence of eating disorders (Erbacher and Bertsch 2020; Stutz 2013), and on the other to fatalism about their bodies, their weight and obesity. Early education on the disease and the significance of a healthy lifestyle, already at the moment of diagnosis, is therefore decisive. Individually adapted eating and exercising programmes allow a stable course of the disease to be achieved, without aggravating increases in volume and weight (Forner-Cordero et al. 2021). The focus should not be on reaching an ideal body weight, but on pain reduction, physical well-being and physical fitness.

Recommendation 10.7

	Degree of recommendation	Consensus
Patients **shall** be informed that eating habits have favourable or unfavourable effects on blood sugar and insulin levels, and therefore on lipogenesis and inflammatory processes.	↑↑	Consensus (94.7%)

10.1 General Measures for Reduction in cases of additional Obesity and Inflammation

High insulin levels foster lipogenesis, exacerbate sodium and water retention, and produce inflammation (Blüher et al. 2005; Feinman et al. 2015; Shoelson et al. 2007). Thus, a diet that avoids blood sugar and insulin peaks, with sufficient pauses between meals, is recommended for reducing overweight and countering inflammatory processes (Amato 2020).

Neuhouser et al. (2012), in a randomised crossover study (n = 40 with BMI of 18 to 24.5 kg/m^2 and n = 40 with BMI of 28 to 40 kg/m^2), investigated inflammatory and obesity-related biomarkers under an isocaloric diet with high or low glycaemic load. Subjects with high fat mass on a low glycaemic diet showed a significant reduction of around 27% in hs-CRP, while their adiponectin increased.

Ruth et al. (2013) randomised obese patients between a hypocaloric High Fat Low Carb diet (HFLC, n = 26) and a Low Fat High Carb diet (LFHC, n = 29) over 12 weeks. While no difference was observed between the groups for weight loss, lean tissue and fat mass, blood pressure, HBA1C, and fasting insulin and glucose levels, significantly stronger effects were found in the HFLC group for the drop in triglycerides and hs-CRP, and the increase in HDL and adiponectin.

10.2 Special diets for lipoedema patients

Recommendation 10.8

	Degree of recommendation	Consensus
A “mediterranean” (if appropriate hypocaloric) diet **can** be recommended on account of its anti-inflammatory properties.	↔	Strong consensus (100%)

There are few case reports of special diets in lipoedema, and only small, non-randomised prospective and retrospective observation studies, mostly with no control group.

Based on the hypothesis that chronic silent inflammation plays a pathophysiological role not only in obesity but also in lipoedema, and that pro- and anti-inflammatory factors can affect the symptoms, various authors recommend focusing on diets that fight inflammation. This can be done by raising patient awareness of pro-inflammatory triggers and recommending an anti-inflammatory and/or ketogenic diet (Amato 2020; Amato and Benitti 2021; Cannataro et al. 2019; Cannataro and Cione 2020; Di Renzo et al. 2021; Faerber 2017a; Faerber 2017b; Faerber 2018). The authors also recommend supplementation with anti-inflammatory micronutrients like Vitamin D and EPA and DHA omega 3 fatty acids, adjusted to the respective blood levels (Amato and Benitti 2021; Calder 2017; Cannataro and Cione 2020; Carracedo et al. 2019).

A case report discusses five conservatively treated lipoedema patients in stages I-IV (Amato and Benitti 2021). In addition to various physiotherapeutic measures, all received an anti-inflammatory diet (not described in detail) and supplementation with antioxidants; one patient subsequently switched to a ketogenic diet. The improvement in the symptoms was assessed with the Lipoedema Symptom Assessment Questionnaire (QuASiL), and was found to be between 35% and 78%. After as little as one month, the volume reduction – depending on the stage of the disease – was between 1,230 mL and over 10,000 mL. The authors postulate in their Conclusions that non-surgical treatment of lipoedema by an interdisciplinary, patient-centred procedure including different professional groups may be successful.

Di Renzo et al. (2021) investigated the effects of a modified, hypocaloric mediterranean diet (mMeD, calorie deficit 20%) for four weeks in 29 patients, (n = 14 in the lipoedema group; n = 15 in the control group) on body weight and body composition, and on alterations in the general state of health, experience of pain, tiredness and functionality in the everyday life of the lipoedema group. The groups did not differ in relation to BMI but to the waist-to-hip ratio. Both groups showed a significant reduction in body weight and BMI. The lipoedema group showed a significant reduction in fat mass in the upper ($p = 0.048$) and lower limbs ($p = 0.007$). There was no difference in lean mass between the groups. In the lipoedema group, the reduction in fat mass in the limbs led to an improved ability to carry out everyday physical activities, which resulted in a significant improvement in quality of life (from 8.3 +-1.8 to 6.9 ±1.4, $p < 0.05$) measured by the European Quality of Life tool (EQ-5D). The authors concluded that these results, for the first time, demonstrated the effectiveness of the mMeD both in reducing lipoedema adipose tissue and in improving physical capabilities.

Recommendation 10.9

	Degree of recommendation	Consensus
A ketogenic (if appropriate hypocaloric) diet **can** be recommended because weight-reducing, anti-inflammatory, and symptom-reducing effects have been described.	↔	Consensus (94.7%)

For the different forms of ketogenic diet, the reader is referred to the S1 Guidelines, Ketogenic Diets, of the Gesellschaft für Neuropädiatrie (AWMF, Nr. 022-021, 2021).

In a detailed review, the authors propose several hypotheses on the effects of a ketogenic diet (KD) on lipoedema (Keith et al. 2021). The effects observed include weight reduction and adipose tissue reduction in the areas typically affected by lipoedema, pain-reduction independent of weight-loss, and improvement in quality of life. They also postulate, among other effects, an anti-inflammatory impact derived from beta-hydroxybutyrate (BHB) and positive effects related to the interaction between metabolic and hormonal alterations, namely between oestradiol and insulin. They conclude that ketogenic diets should be further investigated as a very promising form of treatment for lipoedema.

In another overview report, the authors propose the hypothesis that a ketogenic diet is more effective than other diets in lipoedema, precisely because it combats or prevents inflammation more effectively due to the total absence of pro-inflammatory glucose peaks (Cannataro and Cione 2020).

In a case report, the same authors discuss the case of an obese lipoedema patient who, over a 22-month course of nutritional therapy with a hypocaloric KD (-250 kcal), reduced her weight by 41 kilograms, all her circumference measurements and her pain (VAS reduced from 9.2 to 3, i.e. -67.39%) (Cannataro et al. 2021). All the Quality of Life questionnaires used showed significant improvements (RAND36 in all domains, WOMAC -53.33%, SQS -48.65%). The insulin resistance measured by HOMA-IR dropped from 7.16 to 2.44. The authors see in this treatment a first step towards a special KD protocol for lipoedema.

A Polish work group compared the effects of a Low Carbohydrate, High Fat (LCHF) diet with those of a Moderate Carbohydrate, Moderate Fat (MCMF) diet, with low glycaemic index, on the body composition of 91 lipoedema patients (Jeziorek et al. 2022). 44% of the patients had Stage I lipoedema, 42% Stage II and 13% Stage III. The patients were assigned to a group with one of the two diets over 16 weeks, receiving detailed diet plans. Both diets were designed with an energy deficit ranging from 15 to 25%, according to the patient's degree of obesity; they also included a high content of anti-inflammatory micronutrients and mono- and poly-unsaturated fatty acids.

The subjects' height, body weight, bodyfat percentage, fat mass, lean mass, visceral fat distribution and limb circumferences were measured at the start and finish of the observation period. There was no difference between the anthropometric data of the two groups at the start of the study. All the anthropometric parameters were smaller in both groups after 16 weeks, except for the right distal lower leg circumference in the MCMF group.

Nevertheless, the LCHF group showed larger reductions, with statistically significant differences, in body weight (-8.2 ± 4.1 kg vs -2.1 ± 1.0 kg; $p < 0.0001$), fat mass (-6.4 ± 3.2 kg vs 1.6 ± 0.8 kg; $p < 0.0001$), waist circumference (-7.8 ± 3.9 cm vs -2.3 ± 1.1 cm; $p < 0.0001$), hip circumference (-7.4 ± 3.7 cm vs -2.5 ± 1.3 cm; $p < 0.0001$), as well as thigh and lower leg circumference, than the MFMC group.

The disproportion between upper and lower body was reduced, again less clearly in the MCMF group. Pain and oedema reductions were also observed, as well as improvements in mobility and subjective quality of life in the LCHF group, but not in the MCMF group. The data for these aspects were not published.

A further prospective study compared the effects of a personalised ketogenic diet with calorie reduction of 15-25% over seven months on metabolically relevant laboratory parameters of patients with overweight or obesity (n=24) versus patients with lipoedema (n=24) (Jeziorek et al. 2023). 54% of the lipoedema patients were in Stage II. At the start of the study, the waist circumference of the overweight group was clearly larger than that of the lipoedema group, however this was not the case for body weight or hip and leg circumferences; the waist-to-hip ratio was lower in the lipoedema group. There were also no differences in the laboratory values between the groups, except for significantly higher LDL-C values in the overweight group.

Both groups reduced their body weight. While triglycerides were significantly reduced and HDL-cholesterol increased, the effect on LDL-C varied between individuals. Liver values, glucose tolerance and fasting insulin improved in both groups, although less in the lipoedema group. Kidney and thyroid values remained unaltered in both groups. From these results, the authors conclude that a Low Carb High Fat diet can be a valuable strategy for both lipoedema and overweight patients, since it has a positive effect on body weight, glucose profile, liver values and HDL, without affecting thyroid or kidney function; moreover, it has anti-inflammatory effects.

Faerber has reported several times on the effectiveness of such a ketogenic diet on leg volumes, weight, and pain reduction (Faerber 2017a; Faerber 2017b; Faerber 2018). In a retrospective study of 92 lipoedema patients, painful symptoms measured on a NRS reduced from 6.5 ± 3 to 2 ±2 (- 69.23%, $p<0.01$), independent of weight loss; the same result was reported in normal weight patients. All the circumferences measured were very significantly reduced (between 9.64% in the lower leg and 12.83% in the proximal thigh; $p < 0.001$; effect size -0.93 to -1.27). Subjective reduction in feelings of heaviness and tension occurred after only a few days, and long before significant weight loss. The same was true of tissue alterations reported by the physiotherapists treating the patients.

There are several studies of ketogenic diets tested in rodents which report positive effects on pain (Cooper et al. 2018; Masino and Ruskin 2013; Ruskin et al. 2021).

Sørlie et al. carried out a pilot study on the effect of a normocaloric KD on pain and quality of life in overweight lipoedema patients (BMI 30 -45 KG/ m^2) (Sørlie et al. 2022). The study suffered limitations: a small number of cases (n = 9) and the lack of a control group. The authors therefore consider that the results need to be treated with caution, since the mere fact of participating in the study might have had an effect.

The patients received a normocaloric ketogenic diet for 7 weeks, plus, subsequently, a six-week diet following the Nordic Nutrition Recommendations (NNR). Pain (VAS) and QoL (Norwegian Questionnaire for Lymphedema of the Limbs), weight and body composition were measured at the start and after 7 and 13 weeks. The patients lost weight up to week 7, despite the absence of a calorie deficit (4.6 ± 0.7 kg, $p < 0.001$), partly due to a reduction in total body water (TBW). The pain intensity (VAS) improved by 2.3 ± 0.4 cm ($p = 0.020$). The degree of pain reduction showed no correlation with the weight loss at week seven which was maintained until week 13, while the pain level rose again to the original level in week 13. The authors saw this as confirmation that the pain reduction was attributable to the KD and not the weight loss. It is not clear whether the cause were the ketones themselves, especially Beta-hydroxybutyrate, or the altered composition of the macro- and micronutrients. A significant improvement was found in the general QoL between baseline and weeks seven (1.0 (95% CI (2.0, 0.001)), $p = 0.050$) and 13 (1.0 95% CI (2.0, 0.001) $p = 0.050$). The authors postulate that a ketogenic diet is associated with a reduction in sensations of pain and an improved QoL in lipoedema patients, and recommend larger randomised studies to confirm these findings.

In a prospective case control study, 56 lipoedema patients and 57 overweight or obese women received a Low Carb High Fat diet with anti-inflammatory properties for seven months (Jeziorek et al. 2023). The trial investigated not only the effects on body composition and leg volumes, but also pain reduction using VAS. While both groups presented comparable reductions in weight and circumferences, the participants in the lipoedema group also showed significantly reduced pain values (VAS 4.6 ± 2.6 vs. 3.0 ± 2.3).

Verde et al. (2023), in a recent review of the effectiveness of a very low-calorie ketogenic diet (VLCKD) in lipoedema, found that the VLCKD – especially in cases of concurrent obesity – was an effective treatment option for lipoedema due to its anti-inflammatory properties; and that the combination of VLCKD with a mediterranean diet could strengthen the positive effects yet further.

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11 Appraisal of Bariatric Therapy in the treatment of Lipoedema Patients

Jodok Fink, Till Hasenberg

Recommendation 11.1

	Degree of	Consensus
The indication for bariatric interventions in patients with lipoedema **shall** comply with the S3 Guidelines "Surgical Treatment of Obesity and Metabolic diseases".	↑↑	Consensus (94.7%)
The waist-to-height ratio **shall** be considered at the time of indication, since in cases of pronounced disproportion BMI alone is insufficient.	↑↑	
A bariatric intervention to reduce weight and leg volumes **should** be considered for patients with lipoedema and BMI ≥ 40 kg/m2.	↑	
A bariatric intervention to reduce weight and leg volumes **can** be considered in patients with lipoedema and BMI ≥ 35 kg/m2 to < 40 kg/m2 and at least one other obesity-associated disease.	↔	

There are very few data on bariatric treatment in lipoedema.

This recommendation was drafted considering the current S3 Guideline: Surgical Treatment of Obesity and Metabolic diseases (DGAV) (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) 2018); the European Guideline: "Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP" (EAES) (Di Lorenzo et al. 2020); and the current US American Guideline: "Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update" (AACE) (Mechanick et al. 2020).

The largest available meta-analysis on the effectiveness of bariatric surgery in patients with obesity compared to conservative weight loss therapy includes 25 randomised controlled studies. This shows a very significant advantage, maintained over time, of bariatric surgery for weight loss (Cheng et al. 2016). In 16 out of 25 studies, the primary end point was associated not with weight but with Type 2 diabetes. Another meta-analysis with a total of 11 randomised controlled studies of 796 patients showed clearly that the patients presented a significantly greater weight loss after bariatric surgery than after conservative treatment (Gloy et al. 2013). The weight loss after bariatric surgery was greater by 27 kg of body weight. There was also a higher remission rate from Type 2 Diabetes mellitus and a greater improvement in quality of life. The principal undesired effects of bariatric surgery in this meta-analysis were iron deficiency anaemia (15%) and re-do operations (8%).

There are no long-term data from randomised studies. The long-term data of a large prospective cohort study likewise show a significant advantage for bariatric surgery over conservative treatment, maintained over time, in weight loss and the incidence of Type 2 diabetes, as well as improved oncological outcomes (Sjöström 2013). A different analysis documents the conservative cohort of the same study over a period of 10 years and the patients' constant, unsuccessful attempts to lose weight: 54.6% showed a weight increase, and only 12.5% showed a loss of over 10% of body weight (Zenténius et al. 2018).

There are no randomised controlled studies of bariatric surgery on lipoedema patients. However, a retrospective cohort study of this patient type shows clearly that lipoedema patients can achieve a similar weight loss to that of the overweight controls after bariatric surgery (Fink et al. 2021).

Further evidence on bariatric surgery for weight loss and improvement of metabolic diseases is compiled and evaluated in the S3 Guidelines: Surgical Treatment of Obesity and Metabolic diseases and the EAES and AACE Guidelines (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) 2018; Di Lorenzo et al. 2020; Mechanick et al. 2020).

All three of the guidelines cited above recommend bariatric surgery independent of concurrent diseases only for a BMI value of 40 kg/m^2 or higher (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) 2018; Di Lorenzo et al. 2020; Mechanick et al. 2020). In patients with BMI between $\geq$ 35 kg/m^2 and < 40 kg/m^2, the DGAV, EAES and AACE Guidelines indicate bariatric surgery only with concurrent obesity-associated accompanying diseases (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) 2018; Di Lorenzo et al. 2020; Mechanick et al. 2020). Lipoedema may be a coincident disease, but according to the S3 Guidelines on Bariatric Treatment, it is not an obesity-associated accompanying disease in the sense of the indication of bariatric surgery. In evaluating a bariatric operation, the disproportional distribution in lipoedema patients with a comparatively smaller waist-to-height ratio (WHtR), and thus possibly a lower metabolic risk, should be considered (Bertsch et al. 2020; Brenner and Cornely 2022; Brenner et al. 2023).

There are few data on the specific effectiveness of bariatric surgery in lipoedema. There are two case reports with four patients each, and one further report dealing with the important medical-legal aspects of diagnosing lipoedema (Bast et al. 2016; Pouwels et al. 2018; Pouwels et al. 2019). The principal sources of data are a retrospective cohort study of 31 patients with lipoedema (Fink et al. 2021) and a retrospective case series with 13 patients (Cornely et al. 2022). The case reports indicate certain limitations affecting bariatric surgery, with some cases where leg volumes remained unchanged despite weight loss (Bast et al. 2016; Pouwels et al. 2018; Pouwels et al. 2019). However, the retrospective cohort study shows clearly that the leg volumes were significantly reduced. The reduction in the leg volumes was comparable with that of control patients without lipoedema (Fink et al. 2021). A set of best practice guidelines for the management of lipoedema from Great Britain also mentions bariatric surgery as a possibility for weight reduction in patients with lipoedema (Hardy and Williams 2017).

Data on lipoedema symptoms (pain) after bariatric surgery are available in a case series of 13 patients, in whom lipoedema was diagnosed soon after bariatric surgery, and the patients were then questioned retrospectively about their symptoms prior to bariatric surgery. Pain was found to persist despite good weight loss (Cornely et al. 2022).

No data exist on the type of bariatric OP available, so no recommendation could be given at the time of the creation of these guidelines.

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12 Operative Treatment of lipoedema

Manuel Cornely, Stefan Rapprich

12.1 Liposuction

Recommendation 12.1

	Degree of recommendation	Consensus
Liposuction **shall** be regarded as the surgical method of choice for lasting reduction of the affected subcutaneous adipose tissue of lipoedema in the legs and arms.	↑↑	Consensus (84.2%)

12.1.1 Indication

Liposuction of pain-free lipohypertrophy of the limbs is outside the scope of these Guidelines.

Recommendation 12.2

	Degree of recommendation	Consensus
The following aspects **shall** be considered in indicating surgical treatment by liposuction of lipoedema in the legs and/or arms: • Documented treatment-resistant pain – No improvement despite conservative forms of treatment • Complications, such as reduced mobility and dermatological or orthopaedic sequelae • Critical indications for waist-to-height ratio (WHtR) over 0.55 and BMI over 40 kg/m^2 • Prior-ranking treatment of coincident obesity • Preoperative decongestion in cases of coincident oedema of different genesis • Strict indication for patients aged under 18 years	↑↑	Consensus (94.4%)

Recommendation 12.3

	Degree of recommendation	Consensus
An indication for liposuction **shall** no longer depend on the current Stage classification, since there is no correlation between the severity of the symptoms and the Stage.	↑↑	Strong consensus (100%)

Liposuction can be used alone or in combination with other treatment options.

If diagnosis of oedema has been clinically confirmed, decompression treatment should be carried out prior to the operation. If no oedema is confirmed, preoperative decompression treatment is not necessary. It has no impact on the results of the liposuction treatment.

Surgeons experienced in liposuction advise that the critical indication parameters are BMI > 40 kg/m² and WHtR over 0.55 (Cornely 2000; Cornely 2010; Cornely and Gensior 2014; Gensior and Cornely 2019; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012; Schmeller and Meier-Vollrath 2007).

In cases of coincident obesity and lipoedema, obesity (Kruppa et al. 2020; Rubin et al. 2012; Wollina and Heinig 2019) shall be treated (Deutsche Adipositas-Gesellschaft e.V. (DAG) 2014). Liposuction of the limbs is **not** a weight reduction method (Bertsch et al. 2020; Sandhofer et al. 2020; Sattler et al. 1997)

Patients with lipoedema may suffer from restriction of movement, which entails further orthopaedic complications (Stutz 2011). The volume reduction achieved by liposuction can correct the malalignment and thus relieve those restrictions (Wright et al. 2023)

Rarely, in pronounced lipoedema, large, slack folds of tissue may remain after successful liposuction; in these cases, final skin-tightening by plastic surgery can be recommended, using a lymph vessel-sparing technique e.g. as per AVELAR (Avelar 1985; Ghods 2019).

12.1.2 Techniques and procedures

Recommendation 12.4

	Degree of recommendation	Consensus
Liposuction **shall** be carried out using a tissue and lymph vessel-sparing technique. The following aspects must be taken into account: • Use of vibration-assisted (PAL) or water-assisted (WAL) liposuction systems • Operation under TLA or general anaesthesia • 1-4 sessions for both legs, 1-2 sessions for both arms • Waiting for at least 60 to 120 minutes after the infiltration of the TLA, to ensure sparing aspiration • Limiting the tumescence solution used to 10 litres (if using the Klein solution with a maximum Lidocaine dose of 45 mg/kg KG). • Maximum aspiration volume 10% of body weight	↑↑	Consensus (94.4%)

To spare the lymphatic system in so far as possible, liposuction should be carried out under local anaesthesia using TLA, which prepares the adipose tissue; in other words, using the wet technique with blunt microcannulas (Cornely 2000; Cornely 2006; Cornely 2003; Cornely 2020; Cornely and Gensior 2014; Klein 1987; Klein 2000; Rapprich et al. 2015; Rapprich et al. 2011; Rapprich et al. 2002; Sandhofer et al.; Sattler et al. 1997 2002; Schmeller and Meier-Vollrath 2007; Wollina and Heinig 2019, Wright et al 2023). Supporting techniques like vibration- or water-assisted systems can be used (Stutz and Krahl 2009; Taufig 2003; Taufig 2004). The patient may be ambulatory or admitted to the hospital for surgery (Arbeitskreis "Krankenhaus- & Praxishygiene" der AWMF 2018; Cornely 2000; Cornely 2014; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012). If the operation is carried out under TLA, additional analgosedation may make the operation easier for both the patient and the surgeon.

Anatomical and clinical studies, functional lymphoscintigraphy and immunohistochemical tests of the adipose tissue aspirates confirm that no serious damage occurs to the lymph vessels (Bender et al. 2007; Frick et al. 1999; Hoffmann et al. 2004; Schmeller et al. 2006; Stutz and Krahl 2009; van de Pas et al. 2020). No such studies are available for dry liposuction under general anaesthesia.

Liposuction can also be carried out using the “(super) wet technique” (Dadras et al. 2017; Kruppa et al. 2022; Schlosshauer et al. 2021; Witte et al. 2020).

Regardless of the technique, sparing aspiration can be recognised by the yellow colour of the aspirate, meaning that it contains little blood (Cornely 2023; Cornely et al. 2022; Ghods and Kruppa 2018; Korsake and Rapprich 2020; Kruppa et al. 2022; Sandhofer et al. 2020).

Correctly carried-out liposuction involves subcutaneous, suprafascial, subtotal exhairesis of adipose tissue by aspiration. However, it must not lead to thinning of the skin, since such a radical procedure is not necessary for the objective of pain relief. More radical treatment is linked with a greater risk of complications (Cornely 2016; Korsake and Rapprich 2020; Sandhofer et al. 2020; Sattler and Eichner 2013).

12.1.3 Post-treatment and Outcomes

Recommendation 12.5

	Degree of recommendation	Consensus
Complex physical decongestive therapy **should** be carried out immediately after liposuction. Its intensity and duration should be determined by the postoperative findings. CDT should begin with Phase I.	↑	Strong consensus (100%)

Recommendation 12.6

	Degree of recommendation	Consensus
Conservative treatment of the patients **shall** be continued after liposuction, dependent on their symptoms. Special attention **shall** be paid to mobility, weight stability and stress regulation.	↑↑ ↑↑	Consensus (94.4%)

Lipoedema cannot be cured by liposuction. However, liposuction **can** bring permanent pain relief and improved quality of life.	↔	

The operation leads to express improvements in spontaneous pain, pressure pain and propensity to bruising, with significant differences between pre- and postoperative conditions (Cornely 2000; Cornely 2010; Cornely 2014; Gensior and Cornely 2019; Peprah and MacDougall 2019; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012; Schmeller and Meier-Vollrath 2007; Schmeller and Meier Vollrath 2007). The need for conservative treatment is reduced and to some extent eliminated (Cornely 2004; Cornely 2014; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012). In most cases, the improvements of signs and symptoms are reported to persist for many years (Baumgartner 2014; Baumgartner and Frambach 2016; Cornely 2010; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012; Wollina and Heinig 2019; Herbst et al. 2021, Cornely 2022).

In two operations centres in Germany, the success rates of the above techniques are between 92% and 97%, with postoperative observation periods of up to 15 years in over 325 patients and no reported recurrence (Cornely 2004; Cornely 2007; Cornely 2014; Rapprich et al. 2015; Rapprich et al. 2011).

Although the morphological stage classification does not record the severity of the disease (Brenner 2023, Cornely 2023, Brenner et al 2023), the operation outcomes are better in in the earlier stages than in Stage 3 (Kruppa et al. 2022).

Furthermore, as a result of the reduction of adipose tissue deposits on the inside of the thighs and knees, mechanical and occlusive skin damage is eliminated. Correction of leg malalignment caused by the fat deposits results in improved mobility and gait (Stutz 2011) as well as reduced risk of further orthopaedic complications resulting from lipoedema-associated pathological gait (e.g. hip and knee arthrosis).

The patients' quality of life is clearly improved by the reduction in the symptoms, the increase in mobility, the reduced time devoted to conservative treatment and their improved self-confidence (Blome et al. 2014; Gensior and Cornely 2019; Meier-Vollrath et al. 2005; Rapprich et al. 2015; Rapprich et al. 2011, Seefeldt et al 2023, Kirstein et al 2023, Dahlberg et al 2024)

Complications after medically or cosmetically indicated liposuction have been reported, but are rare.

- An American multi-centre study dated 1995 of 15,336 liposuctions under TLA reported a complication rate of 1.12% (Hanke et al. 1995).
- In a series of 3,240 operations, there were no deaths and no complications requiring hospital admission. In nine cases (0.27%) complications occurred which required further measures (Habbema 2009).

- Kruppa et al. (2020) report a complication rate of approx. 9.5% for all liposuctions. Of these, 1% were bleeding complications, 4.5% wound infections and 4% the development of erysipelas, and therefore not conditioned by liposuction (Kruppa et al. 2020).
- In a later retrospective study in 2022, Kruppa et al. state a complication rate of around 2.3% for all liposuctions. Of these, 0.3% were bleeding complications, 1.3% wound infections and 0.7% the development of seroma (Kruppa et al. 2022).
- Kanapathy et al. reported on 3,583 patients in a meta-analysis. The total incidence of major surgical complications was 3.35%. The total incidence of minor surgical complications was 11.62%, the most frequent minor complication being seroma (5.51%) (Kanapathy et al. 2021).

Complications after liposuction caused by damage to lymphatic vessels are almost never perceived, and therefore reported even more rarely or not at all in the literature (Sandhofer et al. 2020). The reported incidence of swellings that persisted for more than 6 weeks after liposuction is 1.7% (Dixit and Wagh 2013).

These swellings may represent slow healing, but could also include patients with lymphatic vessel injuries. Most of the skin complications after liposuction reported to date begin with hyperaemia and/or skin pallor, followed by skin necrosis and ulceration in the early postoperative phase, or are connected with infection and/or inadequate skin healing. Wright reported on three women with lipoedema who developed lymphoedema after liposuction. The typical skin alterations only appeared 6 - 12 months after the operation and corresponded to the definition of chronic skin alterations in lymphoedema (Wright and Herbst 2022).

Lipoedema-reducing surgery is therefore not entirely risk-free, and can lead to long-term complications, including damage to the lymphatic system (Herbst et al. 2021b; Wollina and Heinig 2019). This may also be attributable to the operative technique:

- In a study in which the lower limbs of fresh cadavers were investigated, dry liposuction with blunt cannulas using longitudinal technique caused moderate or no damage to the lymphatic collectors (Frick et al. 1999; Hoffmann et al. 2004).
- On the other hand, the use of transverse technique regularly caused moderate to severe damage to the lymphatic vessels. In liposuction under tumescence anaesthesia, the longitudinal technique caused moderate or no damage and the transverse technique seldom caused severe damage.
- In liposuction under general anaesthetic and/or with relatively small subcutaneous infiltration, there is an increased risk of damaging the lymphatic system (Wright and Herbst 2022).

In the USA likewise, complications after lipoedema reduction surgery are seldom reported. These complications, as reported by the participants in the investigation, included anaemia, deep leg vein thrombosis, lung embolism, lymphoedema, inflammation of the lung, cellulitis (erysipelas), skin irritation, folds of skin or tissue, asymmetry and slack skin.

The largest percentage of subjects had no complications. In the patients who developed lymphoedema, it is not clear whether this happened as a result of the operation or over the course of time due to an underlying lymphatic disorder. A detailed, long-term, postoperative observation study of patients with lipoedema is needed (Herbst et al. 2021a, Herbst et al. 2021b).

A postoperative investigation in 1,400 lipoedema patients in Germany undergoing surgery under Superwet-TLA and accompanying analgesic or general anaesthesia presented the following distribution of complications: Inflammation 1.79%, seroma 0.79%, erysipelas 0.28%, necrosis 0.14%, thrombosis 0.07% (Cornely 2022).

Schmeller reports an infection rate of 1.4% in 349 liposuctions for lipoedema treatment (Schmeller et al. 2012). Rapprich reports only one case of deep vein thrombosis in 15 years of surgical treatment of lipoedema (Rapprich et al. 2012). In general, liposuction under tumescence carries a low surgical risk, and has proved to be a safe, appropriate procedure.

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13 Appendix 1: Screening

13.1 Screening for important, and frequent, psychological stress, as per the Recommendations of other Guidelines

Clinical questionnaires can be a useful screening tool for assessing the severity of the patients' problems, or for the treating doctor to obtain a more objective impression (Schulte 2011).

Unlicensed questionnaires, freely available through open access, are helpful and practical for everyday practise, and easy to evaluate. In particular, they should make it easier for doctors with no further training in psychotherapy to assess the treatment needs of lipoedema patients.

S3 Guidelines already exist for the diagnosis and treatment of the psychological disorders which are clearly more frequent in women with lipoedema than in the general population (depression, eating disorders and post-traumatic stress disorders) (Dudek et al. 2018; Erbacher and Bertsch 2020). The recommendations given below – which have already been tested in practice in the diagnosis and treatment of women with lipoedema – are consistent with the recommendations of the S3 Guidelines for Diagnosis and Treatment of Unipolar Depression (DGPPN et al. 2015), Diagnosis and Treatment of Eating disorders (DGPM et al. 2018) and Diagnosis and Treatment of Post-traumatic Stress Disorder (Schäfer et al. 2019) (as at January 2021).

In general, de-pathologising the patient's thoughts, feelings and behaviour is of the greatest importance in any psycho-diagnostic screening. For example, in contexts of psychological stress, uncontrolled eating/eating attacks might be described as a "coping strategy", a "psyche-saving strategy" or "a way of coping with stress". A normalised description of the function of the symptoms (e.g. "eating attacks") makes it easier for the patient to open up. It is then easier to talk about difficult subjects, often associated with feelings of guilt or shame, such as loss of control when eating (as in eating attacks) (DGPM et al. 2018).

Patients suffering a psychological disorder, such as depression, often do not report it themselves. It is therefore necessary to ask proactively about depression in particular (DGPPN et al. 2015). Treating doctors who have no psychotherapy training and suspect a picture of psychological disorder can then refer the patient to the relevant specialist (a psychological or medical psychotherapist).

As a rule, the psychological conditions or disorders presented by women with lipoedema are quite easily altered. Experience shows that this information is a great psychological relief for the patient.

The screening diagnoses mentioned below represent a selection of appropriate procedures which can be used for diagnosis and control of the course of the condition. They are applied on the user's responsibility. Screening is no substitute for psychodiagnosis by a professional psychotherapist or psychiatrist, or a psychological psychotherapist.

13.1.1 Screening for lipoedema-associated pain:

- **Visual Analogue Scale** (VAS) (Funke 2010) for assessing lipoedema-associated pain, also recommended in the Lipoedema Guidelines of the Dutch Society for Dermatology and Venerology (NVDV) (2014). This is a 10 cm-long linear scale, on which the patient estimates her pain intensity between 0 "no pain" and 10 "the worst pain imaginable like the pain of amputation":
    - Ask about the maximum pain intensity in a certain period (e.g. the last week)

- Ask about the minimum pain intensity in a certain period (e.g. the last week)

To complement the estimated pain intensity, **Subjective Units of Disturbance (SUD)** can also be assessed with the VAS:

- How badly do you suffer with these pains (scale of 0-10)?

Even at a lower pain intensity, this pain can have a quality that many women with lipoedema find excruciating. On the other hand, there are some (fewer) women with lipoedema who estimate the pain experienced as strong, but their suffering from the pain as slight or moderate.

13.1.2 Screening for Depression:

Two-Question Test, a very time-saving pre-screening method; according to the S3/NVL Unipolar Depression (DGPPN et al. 2015), it identifies unipolar depression with a sensitivity of 96% and a specificity of 57% (Whooley et al. 1997):

1. Have you felt down or depressed or hopeless in the last month?
2. Have you been bothered by having little interest or pleasure in doing things in the last month?

Hospital Anxiety and Depression Scale (HADS) (Bjelland et al. 2002; Zigmond and Snaith 1983), a frequently used procedure; however, it presents a risk of higher positive results even where clinically manifest depression does not exist, i.e. False Positives.

The cut-off values used are: ≤ 7: clinically unremarkable, 8-10: suspect, >10: clinically important depressive syndrome.

13.1.3 Screening for Eating disorders

Eating Disorder Examination - Questionnaire (EDE-Q) (Fairburn et al. 2014 ; Hilbert et al. 2012 ; Hilbert and Tuschen-Caffier 2016 ; Hilbert et al. 2004).

The EDE-Q consists of 4 subscales (22 items). The Restraint Eating and Eating Concern subscales describe remarkable aspects of eating behaviour, results of following a diet or feelings of guilt when eating. The Weight Concern and Shape Concern scales explore whether the subject has a negative body image, and whether her figure and weight are of great importance for her self-esteem. The Questionnaire also asks about eating attacks and compensatory measures.

Download from: https://docplayer.org/24385400-Eating-disorder-examination.html

13.1.4 Quality of life assessment

- **SF-36** to assess the Health-Related Quality of Life (Bullinger 2000; Morfeld et al. 2011). This instrument is frequently used for investigating, and controlling the course of, the subject's quality of life. It has been confirmed as appropriate for assessing the quality of life of women with lipoedema as compared to subjects with lymphoedema (Angst et al. 2020). It includes eight domains: vitality, physical functioning, bodily pain, general health perceptions, role limitations due to physical health, role limitations due to emotional health, social role functioning, mental health. The SF-36 profiles of various diseases are clearly differentiated, for example between lipoedema patients and patients with fibromyalgia (Angst et al. 2021). The values published by Angst et al. (2021) for women with lipoedema can be used as SF-36 reference values for the time being, until specific reference values for lipoedema are produced.

13.2 References

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