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1 Etiopathogenesis, pathophysiology, pain symptoms

Erich Brenner, Manuel Cornely, Gabriele Faerber

1.1 Definition

Recommendation 1.1

	Recommendation	Agreement
Lipedema **should** be described as a painful, disproportionate, symmetrical disorder of fat tissue distribution in the extremities that occurs almost exclusively in women.	↑↑	Strong consensus (100%)

- Lipedema is always painful. A non-painful disproportionate symmetrical fat distribution disorder is referred to as lipohypertrophy and is not covered by this guideline.
- Lipedema is a disproportionate fat distribution disorder that only affects the extremities. The head, neck, and trunk are not affected.
- Lipedema is a symmetrical fat distribution disorder of the extremities. It symmetrically affects both hips, both thighs, and both lower legs. In the upper extremities, it affects both shoulder regions, upper arms, and forearms. The feet and hands are not affected.
- Lipedema is not caused by obesity and does not cause obesity.
- As with all women, obesity may occur concurrently. However, this concurrent obesity is proportional, meaning that it also affects the trunk.
- Based on this coincidental obesity, obesity-associated lymphedema may develop. This mainly affects the lower extremities.
- Orthostatic congestion can occur, as in all women. However, this is independent of lipedema.

1.2 Historical overview

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

- Lipedema affects almost exclusively women.
- The main complaint is fatty swelling of the legs that has been present for many years and in some cases was first noticed during girlhood.
- Lipedema does not usually affect the feet.
- The enlargement of the limbs is generalized and symmetrical.
- The condition is usually associated with weight gain.
- There have been no recurring episodes of acute cellulitis (erysipelas).
- The swelling below the knees is accentuated when patients are on their feet a lot and in warm weather.
- Pain in the legs is common.
- In many cases, there is a history of a similar condition in other family members.

Such patients are usually very sensitive about the appearance of their limbs. It is likely that there are signs of emotional and physical distress.

Occasionally, a patient feels that her large legs have "ruined her life." Many are "ashamed" of their legs.

In a later article, together with Lester E. Wold, Allen and Hines emphasize that (1) the feet are usually normal in size and configuration, (2) there is moderate to severe sensitivity to finger pressure, and (3) especially at the end of the day, there may be some signs of edema on the legs (Wold et al. 1951). In addition, the authors describe the skin and subcutaneous fat as soft and supple. Generalized obesity may be present, but in most cases the upper body parts are normal in size and contour.

"normal."

The initial authors' findings were expanded to include a description of the condition in the arms of female patients, in whom congenital fat distribution disorder occurs synchronously with the legs in up to 90% of cases, also symmetrically (Ghaben and Scherer 2019; Vishvanath and Gupta 2019; White and Ravussin 2019).

1.3 Possible causes

1.3.1 Female

Since Allen and Hines first described lipedema in 1940, the literature has been almost unanimous in stating that lipedema affects almost exclusively women. This gives rise to two possible pathogenetic factors:

1) An X-linked disorder, and
2) A specifically female hormonal disorder.

1.3.1.1 Genetics

Men are extremely rarely affected by lipedema; only a few case reports can be found in the literature. It is generally assumed that excessive hormonal disorders are responsible for the development of the male form of lipedema; however, there are also case reports without such hormonal disorders (Bertlich et al. 2021; Chen et al. 2004).

In a three-generation family with lipedema, in which the mother of the test subject, three sisters, and a niece were affected, Child et al. performed a linkage analysis with X chromosome markers and excluded all markers on the X chromosome (Child et al. 2010). The authors therefore concluded that autosomal dominant inheritance was the more likely mode of inheritance.

Paolacci et al. (2019) identified several possible candidates for an ideal diagnostic genetic test for genetically determined subcutaneous fat accumulation such as lipedema based on a literature review.

Initial evidence of a genetic basis points to a missense variant in AKR1C1 [p.(Leu213Gln)], the gene that encodes an aldo-keto reductase, which catalyzes the inactivation of progesterone into its inactive form (Michelini et al. 2020). The analyses suggest a partial loss of function of the variant.

The analysis by Grigoriadis et al. (2022) identified genetic loci associated with the lipedema phenotype, which was supported by an independent cohort from the 100,000 Genomes Project. The most important SNP, rs1409440, is located upstream of LHFPL6, which is thought to be involved in lipoma formation. How exactly this is related to lipedema is not yet clear.

1.4 Morphology and function

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

The Kaposi's sign on the toes is negative (Brauer et al. 2015), but can also become positive if lipedema is accompanied by [obesity-associated] lymphedema (Ghods 2021). Beltran and Herbst (2017) also found that the proportion of patients (BMI: 39 kg/m² ± 12 kg/m²) with a positive Kaposi's sign increases with stage.

The subcutis of lipedema patients is significantly less compressible, with compressibility of less than 10% using a standardized weight providing a clear indication of lipedema (Kasseroller and Brenner 2019); however, there are also conflicting data. In another study, which was not conducted using standardized compression, no correlation was found (Hirsch et al. 2018).

The proportion of women with hypermobile joints (Beighton score≥ 5) is significantly higher in lipedema 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). and this proportion increases depending on the stage of lipedema (stage 1: 26.9%, stage 2: 59.5%, stage 3: 66.7%).

Lipedema patients more frequently than obese patients show microaneurysms of the initial lymphatic vessels in the thigh and ankle region (Amann-Vesti et al. 2001). The authors defined a microaneurysm as an initial lymphatic vessel with more than twice the minimum diameter of this vessel. However, the intravascular pressure in the initial lymphatic vessels is normal (Amann-Vesti et al. 2002). Lipedema patients show an abnormal lymphoscintigraphic pattern with a slowing of lymph flow that has some similarities to the changes found in patients with lymphedema. (Bilancini et al. 1995; Boursier et al. 2004) Young female lipedema patients show an increased transport function of the lymphatic vessel system compared to the normal population, while older patients show a significantly lower transport function compared to healthy individuals. (Brauer and Brauer 2005) . The reduction in transport capacity correlates significantly with the duration of symptoms, but not with fat mass or morphological stage (Buso et al. 2022). In fluorescence lymphography, the lymph vessels of the lower extremities of lipedema patients in stages I and II appear dilated with intravascular pooling compared to BMI-matched controls of the same age, but the propulsion performance significantly exceeded that of the controls (Rasmussen et al. 2022). In addition, lipedema patients show elevated systemic levels of VEGF-C (control group: BMI-matched patients; p = 0.02), which increases the permeability of vessels and thus interstitial fluid; surprisingly, despite the elevated VEGF-C levels, no morphological changes in the lymph vessels were observed (Felmerer et al. 2020b).

Szél and Szolnoky have described microangiopathy as an early histological feature of lipoedema (Szél et al. 2014; Szolnoky et al. 2008), which may be due to a primary defect in the endothelial barrier function. However, microangiopathy is not specific and not pathognomonic. Alternatively, hypoxia can lead to increased capillary fragility. Elevated levels of free fatty acids (Kim et al. 2005; Vigili de Kreutzenberg et al. 2000) can lead to endothelial dysfunction and altered transendothelial transport. In a low-oxygen environment, HIF-

[1] BMI is not a favorable parameter for selecting a control group, as it is generally higher in lipedema patients than in healthy subjects and therefore BMI matching favors obese patients.

1a-induced fibrosis (Halberg et al. 2009). In addition to hypoxia, two other effects may also be involved in the manifestation of microangiopathy: adipose hyperplasia and local hypertension in the capillaries, which leads to hyperpermeability (Szél et al. 2014).

The frequently described tendency to develop hematomas is attributed to microangiopathy; there is no association between a tendency to bleed in lipedema patients and a coagulation defect (Sucker et al. 2021).

The tissue dielectric constant in lipedema patients is comparable to that in healthy patients (Birkballe et al. 2014).

Patients with lipedema show increased cerebral blood flow compared to healthy individuals (Petersen et al. 2020).

Lipedema patients have larger atrial and left ventricular dimensions and a larger left ventricular ejection fraction than the control group, with no significant differences in other echocardiography variables (Nemes et al. 2020).

An examination using bioimpedance spectroscopy as a surrogate measurement of fluid content found a decrease in impedance in the arms and legs of patients with increasing stages of lipedema (Crescenzi et al. 2019). The impedance values were always significantly higher in the arms than in the legs. The impedance values in the arms of the healthy control group were in the range of the values of patients with stage 2. However, the impedance values in the legs were slightly higher than the values of patients with stage 1.

The sodium content of the tissue of lipedema patients measured by MRI is significantly higher in the lower extremities, but not in the upper extremities, compared to BMI-adjusted controls. (Crescenzi et al. 2020; Crescenzi et al. 2018)

Several studies have shown that lipedema fat tissue is a highly vascularized and fibrotic tissue with an increase in blood vessels, infiltrated by macrophages and containing hypertrophic adipocytes in normal-weight patients (Al-Ghadban et al. 2019; Child et al. 2010; Precone et al. 2019). In addition, the adipose tissue of lipedema patients shows an increase in the proliferation of adipose tissue-derived stem /progenitor/stromal cells (preadipocytes, Ki67-$^+$ - and CD34-$^+$ -cells) (Al-Ghadban et al. 2019; Suga et al. 2009; Taylor et al. 2004).

Lipedema patients have significantly larger adipocytes than a BMI-matched control group (BMI: L: 27.16 kg/m² ± 2.19 kg/m² vs. K: 28.29 kg/m² ± 3.93 kg/m²; adipocyte area: L: 12,250 ± 2,095 µm² vs. K: 7,389± 1,920 µm²; p< 0.001; adipocyte circumference: L: 415 ± 50.3 µm vs. K: 309± 37 µm; p < 0.001) (Felmerer et al. 2020a).

Overall, there is an increase in CD45-$^+$ -cell infiltration (CD45: common leukocyte antigen) compared to a BMI-matched control group. However, 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, in particular, the predominance of macrophages is consistent with the results of other studies (Al-Ghadban et al. 2019) that clearly distinguish lipedema from lymphedema (Gousopoulos et al. 2016a; Gousopoulos et al. 2016b). Data from Wolf et al. (2022) suggest that lipedema causes a shift of macrophages in adipose tissue toward an immunosuppressive (M2) state.

Stroma/stem cells from lipoaspirates, presumably preadipocytes, show an increase in the number of CD146-$^{+}$ nd endothelial cells/pericyte cells in lipedema patients compared to healthy patients (Priglinger et al. 2017). This suggests that this increase could be a marker for leaky blood and lymph vessels in the adipose tissue of lipedema. The expansion of adipose tissue, which is mediated by an increase in the size of adipocytes (hypertrophy) and/or the proliferation (hyperplasia) and differentiation (adipogenesis) of adipose precursor cells/preadipocytes into mature adipocytes, has been demonstrated in lipedema adipose tissue.

Stem cells derived from lipedema patients showed impaired adipogenesis even in the early stages of in vitro differentiation. Parallel to a strongly reduced cytoplasmic lipid accumulation, significantly lower amounts of adiponectin and leptin were detected in supernatants of lipedema stem cells and adipocytes from lipedema adipose tissue compared to control cells. In addition, lipedema and non-lipedema cells differed in their expression of insulin-like growth factor-1, aromatase (CYP19A1), and interleukin-8, as well as in their proliferative activity. (Bauer et al. 2019b)

Small extracellular vesicles from the stromal vascular fraction (SVF) of lipedematous adipose tissue from three patients show different regulation of microRNAs (µRNA; miR–16-5p, miR-29a-3p, miR-24-3p, miR-454-p, miR–144-5p, miR-130a-3p, let-7c-5p) compared to healthy individuals (Priglinger et al. 2020).

Any differences could be due to several factors, including different techniques used to perform the proliferation and differentiation tests, the use of different liposuction techniques, the site of collection, and the stage of disease of the patients included in the study.

1.5 Pathophysiology

Lipedema patients (n= 10) show abnormal lipid metabolism compared to a BMI-matched control group (n=11) (Felmerer et al. 2020a), but not compared to a sample from the general population (Sanchez-De la Torre et al. 2018):

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

However, four common adipokines (IL-6, IL-18, lipocalin-2, leptin) show no significant changes (Felmerer et al. 2020a). These adipokines are elevated in obese individuals (Esposito et al. 2002; Friedman and Halaas 1998; Ouchi et al. 2011; Wang et al. 2007; Ziccardi et al. 2002), which clearly distinguishes lipedema from obesity (Felmerer et al. 2020a).

There is an altered gene signature with upregulation of various proadipogenic and antiadipogenic genes, while the expression of other typical adipose tissue genes remains unchanged (Felmerer et al. 2020a). One of the differentially expressed genes was upregulated in lipedema patients (CCND1: 2.16-fold increase, p = 0.016), while all other differentially expressed genes were downregulated (CCAAT enhancer-binding protein delta [C/EBP-δ]:
2.7-fold decrease, p< 0.001; CFD: 1.88-fold decrease, p= 0.01; NCOR2: 1.81-fold decrease, p = 0.037; Kruppel-like factor 4 (KLF4): 3.57-fold decrease, p = 0.01). Leptin gene expression is also upregulated in fat cells from the subcutaneous tissue of the thighs of lipedema patients (Al-Ghadban et al. 2020). PPAR-γ expression was significantly increased in lipedema adipocytes differentiated from stem cells from abdominal adipose tissue compared to

corresponding cells from healthy patients (p= 0.03) (Al-Ghadban et al. 2020).

C/EBP-δ is a transcription factor known to be involved in inflammatory responses and associated with estrogen regulation (Mendoza-Villanueva et al. 2016). Its role in adipogenesis has been extensively studied, with proliferation induction of growth-arrested differentiated adipocytes being found (Hishida et al. 2009). It also regulates lymphangiogenesis in a hypoxia-inducible factor 1-α-dependent manner (Min et al. 2011).

KLF4 is required for the development of skin barrier function and is involved in the regulation of lipid metabolism and adipogenesis. Recent work has linked KLF4 to macrophage polarization (Coppo et al. 2016; Liao et al. 2018), a factor that regulates adipose tissue metabolism (Thomas and Apovian 2017).

No significant changes in the expression of genes associated with inflammation were found in stem cells derived from lipedema patients or in differentiated adipocytes (Al-Ghadban et al. 2020).

Ishaq et al. (2021) found significant differences in gene expression and lipid and metabolite profiles in tissue, adipose tissue-derived stem cells, and adipocytes from lipedema patients compared to unaffected controls. Functional assays showed that disrupted Bub1 signaling drives the enhanced proliferation of adipose tissue-derived stem cells in lipedema, suggesting a possible mechanism for the enhanced adipogenesis in lipedema. Bub1 encodes a cell cycle regulator that plays a central role in the kinetochore complex and regulates several histone proteins involved in cell proliferation.

1.6 Hormonal influences

Lipedema occurs almost exclusively in women, with initial symptoms or an increase in symptoms almost always occurring during periods of hormonal change (Szél et al. 2014). During puberty, after pregnancy, and during menopause, there is a physiological estrogen dominance due to anovulatory cycles and a lack or decline in progesterone production. At the same time, these phases, like pregnancy, are characterized by physiological insulin resistance (Hoyt and Falconi 2015). However, there is a lack of reliable data on the hormone status of lipoedema patients or a possible connection with hormone administration.

There are indications of a connection with steroid hormones, especially estrogens or estradiol (Child et al. 2010), the ratio between them and progestogens, especially progesterone, and/or the distribution and function of their receptors (Kalkhoff 1982; Lindberg et al. 1990; Mauvais-Jarvis et al. 2013). These connections could influence both the increase in volume of the subcutaneous fatty tissue and the sensation of pain.

Idiopathic edema or fluid retention syndrome, which should not be confused with lipedema, can occur coincidentally with lipedema and aggravate the symptoms (Pereira de Godoy and Guerreiro Godoy 2022; Pereira de Godoy et al. 2017). These patients may experience symmetrical congestion and generalized swelling that increases during the course of the day, including in the feet, hands, breasts, abdominal area, and face. In addition to increased capillary permeability, a connection has been observed with a disturbed hypothalamic-pituitary axis or estrogen dominance (Young et al. 1983). The water loading test (Streeten

test, Streeten 1997) is not useful for differential diagnosis, as it can be positive in both idiopathic and lipedema.

The following statements are research topics and have not yet been specifically investigated in lipedema patients.

Estrogens promote the typical female subcutaneous fat distribution by increasing insulin secretion and sensitivity in the target tissues, with fat tissue on the hips and thighs being particularly sensitive to estrogen (Lindberg et al. 1990). Depending on the target tissue, they can slow down fatty acid oxidation (Kalkhoff 1982; Mauvais-Jarvis et al. 2013), so that even with systemically low insulin levels, adipogenesis may be enhanced locally, while beta oxidation is prevented (Gower et al. 2002). Estradiol increases the sensitivity of adipose tissue to insulin, so that less insulin is needed to prevent lipolysis (Pereira et al. 2015).
Conversely, insulin stimulates the aromatization of testosterone to estradiol in adipose tissue (Cohen 2001).

In postmenopausal women, estradiol is mainly produced in subcutaneous adipose tissue (Simpson et al. 1997), with aromatase mRNA expression being higher in the buttocks and thighs than in the abdomen and increasing with age everywhere (Bulun and Simpson 1994).

Estrogens and progestogens also exert a modulating effect on the psyche, particularly with regard to anxiety (Kessler et al. 2005). Both can have an antidepressant effect, but while estradiol has an excitatory effect and can promote nervousness and anxiety when there is an imbalance, progestogens, especially pregnenolone and allopregnenolone, have anxiolytic, calming, and sleep-promoting effects (Da Pozzo et al. 2012; Quast et al. 2014).
Neurosteroids also regulate pain perception: progesterone and its derivatives dihydroprogesterone and allopregnenolone have a neuroprotective effect in the central and peripheral nervous system (Joksimovic et al. 2018), and allopregnenolone has been shown to have an analgesic effect in pain models (Coronel et al. 2011). Progesterone is broken down into 20α-OH progesterone by the aldehyde-keto reductases (AKR) 1C1, 2, and 3 (Zhang et al. 2009).
AKR1C1 acts via its enzyme activity as a positive regulator of adipogenesis of human adipose tissue stem cells (adipose-derived mesenchymal stromal/stem cells, ASCs) (Liu et al. 2021). A mutation of AKR1C1 was detected in a family with monogenically inherited lipedema and postulated as the causal gene in this family (Michelini et al. 2020).

Progesterone induces hyperinsulinemia, possibly through direct action on the pancreatic islets, and at the same time promotes glycogen storage in the liver (Kalkhoff 1982). Paradoxically, it counteracts the effect of insulin on glucose metabolism in adipose tissue and skeletal muscle. Progesterone stimulates the deposition of body fat but has catabolic effects on protein metabolism (Kalkhoff 1982). Progesterone increases body weight, leading to obesity, and increases insulin receptor concentration and both basal and insulin-stimulated lipogenesis in adipose tissue without impairing insulin sensitivity (Mendes et al. 1985). The lipogenic effect is based on upregulation of ADD1 / SREBP1c (adipocyte determination and differentiation 1/sterol regulatory element-binding protein 1c) at the transcriptional level (Lacasa et al. 2001). The administration of progesterone to female laboratory animals leads to an increase in the mass of white adipose tissue in the body and in the groin region (Stelmanska et al. 2012). The increased circulating progesterone concentration was associated with an approximately 6- and 2-fold increase in leptin and resistin mRNA levels and a 2-fold decrease in adiponectin mRNA levels only in the adipose tissue of the inguinal region. This effect appears to be limited to females (Stelmanska et al. 2012; Stelmanska and Sucajtys-Szulc 2014). The increased progesterone concentration in the blood was associated with a

significant increase in the expression of lipogenic enzyme genes in the inguinal adipose tissue of female experimental animals (Stelmanska and Swierczynski 2013). The increase in the expression of lipogenic enzyme genes was associated with an increase in the expression of the sterol regulatory element binding transcription factor 1 (Srebf1) and the S14 genes. The administration of progesterone to female experimental animals led to an increase in food intake, body mass, and white adipose tissue mass. Elevated circulating progesterone concentrations led to increased expression of NPY and decreased expression of CART genes in the hypothalamus of women (Stelmanska and Sucajtys-Szulc 2014). In male experimental animals, increased progesterone concentrations in the blood had no effect on food intake, body and fat mass, or the expression of neuropeptide genes in the hypothalamus (Stelmanska and Sucajtys-Szulc 2014).

In a review, Katzer et al. (2021) see two possibilities for increased estrogen-dependent lipogenesis in lipedema: an altered distribution of estrogen receptors in adipocytes (ERα
/ERß ratio) with resulting metabolic signals and/or increased production of enzymes for steroid formation by adipocytes, resulting in increased paracrine release of estrogen. These changes could lead to increased activation of peroxisome proliferator-activated receptor (PPAR), uptake of free fatty acids and glucose into adipocytes, and angiogenesis, while reducing lipolysis, mitochondriogenesis, and mitochondrial function. Taken together, these metabolic changes could lead to increased adipogenesis and thus to an increase in adipose tissue.

An imbalance and/or dysfunction of steroid hormones can therefore contribute to both disturbed fat distribution and increased or reduced pain perception in individuals with a predisposition to this (Bano et al. 2010; Michelini et al. 2020; Xu and Lopez 2018). Persistently elevated cortisol levels due to chronic stress can also contribute to this, as cortisol, which itself lowers the pain threshold (Choi et al. 2012), is produced from progesterone when demand is high, further reducing its antagonistic, stress- and pain-reducing effect.

The significance of these findings for elucidating the pathogenesis of lipoedema cannot be assessed at present. There are currently no studies on lipoedema patients.

Overweight or obese lipedema patients have lower average insulin levels than patients with a comparable BMI but without lipedema (Faerber 2018, Nono Nankam et al. 2022). However, if insulin resistance develops with increasing obesity, this can lead not only to increased lipogenesis and reduced lipolysis, but also to increased hunger and increased food intake (Ludwig and Friedman 2014) (see Chapter 10 Nutrition).

The prevalence of hypothyroidism is significantly higher in lipedema patients, at over 30% to over 40% compared to the average population (2%) (Bauer et al. 2019a; Földi 2009). Steroid hormones also influence the function of thyroid hormones: estradiol negatively, progesterone positively. The influence of potentially coexisting obesity remains to be clarified.

1.7 Symptom: pain

Pain is described as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or resembling it. The experience of pain is influenced by biological, psychological, and social factors to varying degrees. Pain and nociception are distinct phenomena that cannot be derived solely from the activity of sensory neurons; it is assumed that, in addition to the factors mentioned above, personal life experiences also contribute to the concept of pain.

concept of pain. Pain has an adaptive role, but it can nevertheless have negative effects on a person's functioning and social and psychological well-being. Verbal expression is considered the most common behavior among a variety of ways to express pain, alongside motor behavior. (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 multidimensional definition (Melzack and Casey 1968). These dimensions include the sensory-discriminative (intensity, location, quality, and duration), affective-motivational (discomfort and the subsequent escape response), and cognitive-evaluative (evaluation, cultural values, context, and cognitive state) dimensions of pain. These three dimensions are not independent but interact with each other. A person's cognitive state can modulate one or two of these dimensions of pain perception. (Moayedi and Davis 2013)

Pain is the key symptom of lipoedema. On palpation, the pain can be both superficial and subcutaneous. A wide range of clinical observations support a model of slow development of lipoedema pain. The onset of the symptom may not be taken seriously due to its unobtrusive start in the first years of lipoedema development. As the condition progresses, the frequency and intensity of the pain may increase. This needs to be confirmed by scientific studies in the future. The pain associated with lipedema is not limited to individual dermatomes, but can occur around the entire circumference of the legs or arms. (see Chapter 2.2 Diagnosis and differential diagnosis)

However, the pain associated with lipedema has been insufficiently investigated and characterized in the literature, with authors mostly content to offer hypotheses. Hardly any of the tangible findings appear suitable as a basis for explaining the pain associated with lipedema. Looking at the pain in lipedema from the perspective of the pain literature, a mechanical dynamic allodynia, involving Aβ fibers and probably also tactile C (CT) fibers. CT fibers can in principle be stimulated by manual lymphatic drainage (MLD), which could potentially explain the pain-relieving effect of MLD. Conversely, however, this pain-relieving effect via the CT fibers would rule out small fiber neuropathy (SFN) and thus probably any direct nerve damage as the cause of pain. (Brenner 2017)

A questionnaire-based study of 592 patients (response rate: 57%) who underwent liposuction between 1997 and 2012 showed a postoperative improvement in quality of life in 95% of cases, and 97% of patients were able to completely dispense with further complex physical decongestive therapy, even 15 years after the operation (Cornely and Gensior 2014).

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

Another recent retrospective study showed that among the clientele of a German specialist clinic for lymphology, four-fifths of patients diagnosed with lipedema already showed high psychological distress before the onset of lipedema-associated symptoms (Erbacher and Bertsch 2020). This psychological distress included diagnoses such as depression, eating disorders, or post-traumatic stress disorder, and/or serious psychological abnormalities such as burnout syndrome or chronic stress. However, it should be noted that

these were predominantly patients with coincident obesity and that the survey was often conducted long after the first onset of lipedema symptoms.

A recent study of 20 non-obese lipedema patients and 20 control subjects matched according to waist-to-height ratio (WHtR) using the clinically recognized QST protocol of the German Research Association for Neuropathic Pain (DFNS e.V.) shows a different picture (Dinnendahl et al. 2023). The lipedema patients showed no obvious psychometric abnormalities. Lipedema pain tended to manifest as somatic rather than neuropathic or psychosomatic aversions. All QST measurements were normal, with two selective exceptions: the pressure pain threshold (PPT) was greatly reduced and the vibration detection threshold (VDT) was selectively greatly increased on the affected thigh. In contrast, the sensory profiles on the back of the hand were normal. The authors propose evaluating the vibration detection threshold and pressure pain threshold on the dorsal hand and lateral thigh, respectively, as a combined PVTH score, which shows promising potential for lipedema diagnosis (specificity: 96.5%).

A major problem with most studies is the measuring instruments used, which make comparability very difficult due to different parameters and scales. In addition, most of the questionnaires used have not been validated. One exception is a study from 2019 that used the validated pain questionnaire (DSF) in the long version of the German Pain Society (Gensior and Cornely 2019). The pain was
predominantly described as pressing and pulling; overall, the leading symptom of "pain" is very multifaceted. However, the authors found that many questions were only of limited use for lipedema patients, with the result that some patients did not complete the questionnaires in full. Some questions, such as the correlation between the stages of lipedema and the listed changes in quality of life, could not be answered using the evaluation software used.

In summary, the symptom of pain is multifaceted, difficult to define, and influenced by numerous factors. Ultimately, the pathogenesis of pain has not yet been clarified.

Recommendation 1.2.

	Recommendation	Agreement
Due to diverging findings, numerous aspects and parameters of lipoedema **should** be investigated more comprehensively in order to improve the scientific data available.	↑	Strong consensus (94.1%)

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2 Definition, clinical presentation, diagnosis, and differential diagnosis

Tobias Hirsch, Tobias Bertsch

2.1 Definition of the clinical picture

Recommendation 2.1

	Level of recommendation	Agreement
Symptoms of lipoedema include pressure and touch sensitivity, spontaneous pain and a feeling of heaviness.	↑↑	Strong consensus (100%)

Recommendation 2.2

	Recommendation	Agreement
Disproportionate fat tissue accumulation in the extremities without corresponding symptoms **should** not be diagnosed as lipedema.	↑↑	Strong consensus (100%)

The diagnosis of lipoedema requires the presence of disproportionate fat tissue accumulation in the legs, and less frequently in the arms, compared to the trunk, accompanied by symptoms in the area of this disproportionate fat tissue. The symptoms include painful sensations such as pressure pain, spontaneous pain, and a feeling of heaviness.

The term "lipohypertrophy" commonly used in the literature (Herpertz 1995; Reich-Schupke et al. 2013) continues to be used for symptom-free circumferential enlargement of the legs, without the term referring to the exact histological differentiation between hypertrophy and hyperplasia.

2.2 Clinical presentation and course of the disease

2.2.1 Morphology

The disproportion in lipedema always occurs symmetrically on the legs and/or arms (Cornely 2003; Herpertz 2004). Lipedema occurs exclusively on the extremities. Neither the trunk, head, nor neck are affected. There is no scientific evidence for the development of lipedema in other areas of the body, either before or after liposuction.

The fat accumulation can be distributed evenly across the upper and/or lower legs (known as "column legs") or the upper and/or lower arms, or it can only affect the upper or lower legs. The feet and hands are not affected. A typical feature is a difference in caliber between the affected area and the adjacent healthy area (known as "muff" or "collar" formation). Symmetrical, painful accumulations of subcutaneous fatty tissue above and/or below the knees, in the the triceps region of the arm, and on the forearms. These are referred to as "double chins." The morphological picture does not allow any conclusions to be drawn about the subjective symptoms.

Typical morphological features are shown in Table 1. Due to the diverging information in the various sources, no recommendation can be made regarding the use of a numerical typing system for localization.

Table 1: Localization and classification of the affected regions

Localization		According to Herpertz (1995)	according Schrader (2019)	according Beltran and Herbst (2017)	according (Kruppa et al. 2020)
Leg	Lipedema on buttocks/hips		Type	Type I	Type I
	Lipedema up to the knees	Thigh type	Type 2	Type II	Type II
	Lipedema extending to the lower leg	Lower leg type			
	Lipedema extending to the ankles	Ankle type	Type 3	Type III	Type III
	Lipedema only on the lower leg				Type V
Arm	Lipedema on the shoulder				
	Lipedema extending to the upper arm	Upper arm type	Type 4	Type IV	Type IV
	Lipedema extending to the forearm	Forearm type			
"Central"	Lipedema on arms and legs	Upper arm & thigh type			
	Lipedema on arms and legs, predominantly legs			Type V	

Recommendation 2.3

	Recommendation	Agreement
The morphological characteristics **should** be descriptive in nature and **should** not be understood as a classification of severity. .	↑↑	Strong consensus (100%)

Recommendation 2.4

	Recommendation	Agreement
The staging of morphology commonly used in the literature to date **should** not be used as a measure of disease severity. There is currently no staging system for symptoms.	↑↑	Strong consensus (100%)

There is currently no staging system for these symptoms.

Recommendation 2.5

	Recommendation	Agreement
The criterion of "nodular" fatty tissue, which was frequently used in the past, should not be used for diagnosis due to a lack of validity "nodular" adipose tissue **should** not be used for diagnosis due to a lack of validity.	↑↑	Strong consensus (100%)

2.2.2 Symptoms

Physical complaints are reported in the subcutaneous fatty tissue of the affected extremities: pain on touch or pressure, tension and heaviness, spontaneous pain. The intensity of the complaints is perceived very differently by the women affected.

The subjective perception of swelling in the affected extremities during the course of the day plays a special role in the description of symptoms. In a comparative study of symptomatic lipoedema patients and healthy individuals, swelling perceived during the course of the day could not be objectively confirmed, leading the authors to conclude that the feeling of increased circumference must be interpreted as part of the pain experience (Erbacher et al. 2022).

In cases of particularly pronounced disproportionate subcutaneous fat tissue accumulation in the extremities, complications such as static changes such as misalignment of the knee joints (genu valgum) and skin conditions (intertriginous maceration, skin irritation due to skin-on-skin friction) may occur.

In addition to the purely somatic symptoms with disproportionate fat distribution and the above-mentioned complaints, the following coincidences must be given special consideration in lipedema: weight gain and obesity, psychological stress, lack of self-acceptance or
Acceptance of one's own body.

A tendency to develop hematomas is frequently reported (Forner-Cordero et al. 2021), but based on the available studies, it cannot be used as a decisive diagnostic criterion (Herpertz 1995; Sucker et al. 2021; Szolnoky et al. 2017; Szolnoky et al. 2008).

The tendency to develop hematomas frequently reported by lipedema patients could not be objectively confirmed in a comparative clinical study by Erbacher et al. (Erbacher et al. 2023).

Psychological factors can trigger or intensify pain (see also Chapter 8 Psychosocial Therapy).

2.1.1 Weight gain and obesity

In addition to soft tissue complaints and disproportionate fat distribution, a large number of affected women, as assessed by BMI, suffer from obesity. Only a minority are of normal weight (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 common comorbidities of lipedema. Obesity can exacerbate lipedema.

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

The body mass index (BMI) used to characterize overweight is not meaningful in lipedema patients, as it leads to falsely high values in the overweight or mild obesity range due to the extremity-emphasized increase in adipose tissue. A more accurate assessment of disproportionate fat distribution can be obtained by combining BMI with the waist-to-height ratio (WHtR) (Brenner et al. 2023).

Recommendation 2.6

	Recommendation	Agreement
For initial documentation and follow-up, at least the biometric values body weight, height, waist circumference, and hip circumference **should** be recorded.	↑↑	Consensus (94.1%)

Table 2: Recommended biometric measurements

Measure	**Additional explanation (according to WHO, 2022)**	**Unit**	**English Designation**
Body weight	To one decimal place	[kg	(body) weight
Height	Stand straight and with feet hip-width apart apart	[cm	height
Waist	The waist circumference is measured at the midpoint between the lower rib cage and the iliac crest (at level of the spinous process L3)	[cm]	waist circumference
Hip circumference	Measured at the widest point of the buttocks measured with the tape measure parallel to the floor.	[cm]	hip circumference

Recommendation 2.7

	Recommendation	Agreement
Further measurements of the extremities and indices **should be taken** for therapy planning and progress monitoring, depending on the extremities affected.	↑	Strong consensus (100%)

Table 3: Overview of further measurements

Measure	**Supplementary explanation** (CEN/TC 205 2009)	**Unit**
Circumference of proximal thigh	5 cm below the midpoint of the crotch with the patient standing upright patient standing upright; in stocking measurement, this is referred to as cG	[cm]
Circumference mid-thigh	Circumference in the middle of the thigh, between the center of the crotch and the center of the kneecap; in stocking measurement [cm]	[cm]
Proximal calf circumference	Circumference at the narrowest point, just below the shin bone (*tuberositas tibiae*); referred to as cD in sock measurements.	[cm]
Maximum circumference Calf	Calf at its maximum circumference; in the stump measurement, this is referred to as cC. .	[cm]

Circumference Calf insertion	Circumference at the proximal end of the Achilles tendon (approx. 5 cm distal the middle of the calf); referred to as cB[1]in the stocking measurement.	[cm]
Circumference of the distal calf	Ankle circumference, ankle at the point of its smallest circumference, in the stocking measurement, referred to as cB.	[cm]

Recommendation 2.8

	Degree of recommendation	Agreement
The use of the lipohypertrophy quotient according to Herpertz **can** be used to describe the disproportion.	↔	Strong consensus (100%)

Table 4: Calculated measured values

Value	Calculation	Notes
Body mass index	$BMI = \frac{Körpergewicht\ [kg]}{Körpergröße\ [m]^2}$	Attention: Height in meters!
Waist-to-height ratio	$WHtR = \frac{Taillenumfang\ [cm]}{Körpergröße\ [cm]}$	
Waist-to-hip ratio	$WHR = \frac{Taillenumfang\ [cm]}{Hüftumfang [cm]}$	
Lipohypertrophy quotient	$LipQ = \frac{Umfang proximaler\ Oberschenkel\ [cm]}{Körpergröße\ [cm]}$	Calculate separately for both sides .

Table 5: Classification of calculated measured values (Schneider et al. 2010; Stemper 2013; World Health Organization 2000)

		Normal	Overweight	Obesity		
				Grade I	Grade II	Grade III
BMI [kg/m²]		18	25	30	35–40	> 40
WHtR	15–39	0.40 – 0.50	0.51 – 0.56	0.57 0	> 0	
	40–49	+ 0.01 / year of life				
	50 years and older	0.50	0.61 – 0.66	0.67 0	> 0	
WHR	Women	< 0.8	0.8 – 0.84	> 0		
	Men	< 0	0.9	> 0		

Recommendation 2.9

	Recommendation rate	Agreement
During the initial consultation, psychological factors that may play a role in the experience of the clinical picture **should** be identified.	↑	Consensus (94.1%)

2.1.2 Psychological stress

Data indicate that mental health is more severely impaired in lipoedema patients than physical health (Frambach et al. 2015). The vast majority of

Previous publications assumed that the diagnosis of lipedema was the cause of this psychological impairment (Dudek 2017; Dudek et al. 2016; Fetzer and Fetzer 2016). In contrast, *Erbacher* found that the vast majority of 150 female patients in his study had already been experiencing psychological distress before the onset of symptoms typical of lipedema (Erbacher and Bertsch 2020). Psychological distress and self-acceptance issues play a significant role in the disease dynamics of lipedema (see Chapter 8).

2.1.3 Course of the disease

Recommendation 2.10

	Level of recommendation	Agreement
Lipedema **should** not be considered a progressively worsening disease, as progression depends on various factors. factors.	↑↑	Consensu s (94.4%)

Recommendation 2.11

	Recommendation	Agreement
The causes of lipedema progression **should** be investigated individually, depending on the patient.	↑	Strong consensus (100%)

Contrary to previous thinking, lipedema is not fundamentally progressive. There is no scientific evidence to support progression. The first authors to use the term "progression" in this context were *Wold, Allen, and Hines*, who first described lipedema in their publication in 1951. However, even the first authors recognized a clear link between progression and an increase in body weight (Wold et al. 1951).

A recent Spanish study on this issue confirms this correlation with weight gain; in two-thirds of patients, the disease was stable, while in the remaining third, progression was correlated with weight gain (Forner-Cordero et al. 2021). Only with progressive weight gain does the volume of the legs (also) increase. Frambach et al. (2016) also describe this correlation.

Regardless of this, it should be noted that pain symptoms do not correlate with the severity of disproportion or the increase in subcutaneous adipose tissue.

It follows that, with largely stable weight, lipedema is not necessarily progressive, but can remain stable for many years or permanently. However, there are individual trigger factors that can lead to the progression of lipedema, in addition to weight gain, e.g., hormonal influences (e.g., menopause). This affects both the severity of fat tissue gain and disproportion as well as pain symptoms and accompanying psychological factors.

2.2 Diagnosis and differential diagnosis

2.2.1 Differentiation between lipedema and lymphedema

Table 6: Differential diagnosis of adipose tissue disorders

	Lipedema	Lipohypertrophy	Obesity	Lymphedema
Fat accumulation	+++	+++	+++	(+)
Disproportion of the extremities to the trunk	+++	+++	(+)	+
Edema	ø	ø	(+)	+++
pressure pain	+++	ø	ø	ø
Symmetry	+	+	+	ø

Recommendation 2.12

	Recommendation	Agreement
The diagnosis of lipedema **should** be made clinically.	↑↑	Strong consensus (100%)

The reason for this is that there are no definitive instrumental or laboratory tests that can prove the diagnosis of lipedema.

2.2.2 Significance of diagnostic methods and differential diagnoses

Recommendation

	Level of recommendation	Agreement
Instrumental examination methods **can** be used for differential diagnosis.	↔	Strong consensus (100

The differential diagnosis of lipoedema from conditions such as CVI, obesity and lymphoedema, but also lipohypertrophy of the extremities without pathological significance, is sometimes difficult to make on the basis of physical examination and medical history alone.

There is only limited data with a low level of evidence available on imaging techniques and laboratory chemical measurement methods. Various studies on ultrasound diagnostics, MR angiography, scintigraphy, and indocyanine green lymphography have been published in recent years.

2.2.3 Ultrasound diagnostics

Recommendation 2.14

	Level of recommendation	Agreement
Ultrasound diagnostics can be used to rule out edema, e.g., of phlebological origin. Ultrasound diagnostics **can** be used.	↔	Strong consensus (100%)

Recommendation 2.15

	Recommendation	Agreement
Conclusions about the etiology of subcutaneous edema **should not be drawn** not be drawn from B-mode sonography of the edema.	↑↑	Strong consensus (100%)

In the context of lipedema diagnosis, duplex sonography is only relevant for identifying vascular differential diagnoses and comorbidities such as varicose veins, post-thrombotic syndrome, or compression syndromes.

While duplex sonography provides very accurate information about vascular function, B-mode sonography can be used to distinguish between solid and liquid tissue structures. Blood vessels, fluid-filled cysts, and effusions are identified by the absence of internal echoes. In this way, edema can be visualized as three-dimensional, echoless tissue gaps (Marshall and Schwahn-Schreiber 2008). It is not possible to determine the etiology of edema based on ultrasound findings (Becker et al. 2015).

Naouri et al. (2010) compared the echogenicity and thickness of the cutis and subcutis in patients with lipedema and lymphedema and a healthy control group. While sonographic differentiation of lymphoedema was possible due to reduced echogenicity of the cutis with increased thickness, lipoedema could not be reliably distinguished from the tissue of the healthy control group.

Similar to the findings of Naouri et al. (2010), Hirsch et al. (2018) concluded that it is not possible to distinguish between the cutaneous and subcutaneous ultrasound findings of lipedema and normal findings or findings of lipohypertrophy or obesity. Both groups of authors emphasized that it was not possible to identify an edema component in the group of subjects with lipedema using high-resolution ultrasound (Hirsch et al. 2018).

The results were also confirmed by Iker et al. (2019). Using additional analysis software, the working group also found evidence that the subcutis in the lipedema group was not only thicker than in the comparison group, but also significantly less echogenic than in the lymphedema group and the healthy control group. The study was limited by 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 reduced compressibility in sonographic measurements of subcutaneous thickness in a small cohort (n = 69) of patients with lipedema compared to healthy individuals. The control groups consisted of non-lipedema patients (n= 12) and men (n = 7) (Kasseroller and Brenner 2019).

Overall, it can be concluded that defined sonomorphological criteria for the echogenicity of the subcutis in lipedema and reliable cut-off values for compressibility are currently not available. Sonographic criteria that indicate the presence of edema are not met in lipedema.

2.2.4 Sectional imaging (computed tomography/magnetic resonance imaging)

Computed tomography cannot provide specific evidence of lipedema (Monnin-Delhom et al. 2002).

Magnetic resonance imaging and MR lymphangiography are used to detect and quantify liquid components of tissue or interstitial fluid. Various studies have been published on the morphology of lipedema and so-called "lipolymphoedema." In addition to an increase in subcutaneous fatty tissue with a homogeneous texture, the MR examination by Cellina et al. (2020) also found no edema in patients with pure lipedema. They found dilated peripheral lymph vessels in patients with lipedema and additional lymphedema (Cellina et al. 2020). One limitation of the study is that it included only overweight subjects (BMI > 31 kg/m²) and no phlebological diagnosis was performed on the individuals included, so that the results do not provide any information as to whether the subjects with so-called "lipolymphedema" are not in fact suffering from obesity-associated concomitant edema (lymphoedema, phleboedema).

Lohrmann et al. (2009) performed MR lymphangiography on patients with lipedema and "lipolymphoedema" (n= 13). In the group of subjects with "lipolymphoedema," whereas in pure lipoedema, these were only measurable with calibres of up to 2 mm. They interpreted these calibre changes as indications of incipient lymphostatic decompensation in lipoedema. The entity of so-called "lipolymphoedema" is also not defined in more detail in the study, so it is also unclear whether this is lipoedema with additional lymphoedema or obesity-related lymphoedema (Lohrmann et al. 2009).

Crescenzi et al. (2020; 2018) demonstrated in comparative studies on lipedema patients (n = 10) in stages I and II with a control group (matched according to BMI and lower leg circumference) and obese female subjects showed that women with lipedema have increased sodium levels and an increased fat/water ratio in the skin and subcutaneous fatty tissue. The diagnostic potential of this study is limited by the small number of cases and further limitations in the study design. Due to space constraints in the MRI scanner, subjects with particularly pronounced lipedema or severe obesity in the control group could not be included. The individuals examined also had a variety of previous treatments, ranging from complex physical decongestion to liposuction and gastric reduction (Crescenzi et al. 2020; Crescenzi et al. 2018).

2.2.5 Indirect functional lymphoscintigraphy:

A study using lymphoscintigraphy concluded that, in contrast to lymphoedema, lipoedema may initially be associated with increased lymph transport, which decreases disproportionately with age compared to healthy individuals (Brauer 2000; Brauer and Brauer 2005). These studies are not BMI-matched.

There are no systematic studies on the differential diagnosis of lipedema using lymphoscintigraphy. Forner-Cordero et al. (2018) examined lipedema patients using lymphoscintigraphy and found that changes in

radionuclide patterns. There was no correlation with the symptoms or severity of lipoedema. The study has some limitations. On the one hand, the distinction between subjects with lipoedema and those with lymphoedema was unclear. In addition, the women examined were up to 80 years old. Forner-Cordero et al. confirmed that lymphatic function declines with increasing age, even in healthy people (Forner-Cordero et al. 2018). The decisive factors here are the age-related loss of glycocalyx and the increased production of proinflammatory 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 lipedema diagnostics

There is only limited data available on newer diagnostic methods such as ICG-L and NIRF-LI in small cohorts of lipedema patients. At present, these methods cannot contribute to confirming a diagnosis of lipedema. However, the results of the available studies suggest that there is no lymphatic drainage disorder in lipedema (Buso et al. 2022; Rasmussen et al. 2022).

The absence of lymphatic insufficiency in patients with lipedema is also confirmed in a recent study by the ALERT group at Macquarie University Sydney. Of 40 patients diagnosed with lipedema who were examined using ICG, only 2 patients showed lymphatic insufficiency (dermal back flow). One of these two patients already had a history of primary lymphedema, while the second had grade 2 obesity, leading the authors to assume an obesity-associated edema component (Mackie et al. 2023).

In their study, the Australian colleagues also discuss the dilation of lymph vessels in patients with lipedema, which is occasionally described in ICG findings. The spatial resolution of ICG lymphography decreases rapidly under the skin, leading to a distortion of the geometry of the lymph vessels. Although the lymphatic vessels may appear dilated when located deep in the overlying adipose tissue, this should not be considered abnormal dilation of the lymphatic vessels, but rather a known optical scattering property of ICG lymphography (Mackie et al. 2023; Weiler et al. 2012).

2.2.7 Laboratory chemical methods

Recommendation 2.16

	Recommendation rate	Agreement
Laboratory parameters **can be used** to rule out differential diagnoses, but are not suitable for proving lipedema.	↔	Strong consensus (94.4%)

Laboratory chemical methods for identifying lipedema or for differential diagnosis are not currently available. In the context of edema diagnosis, routine internal medicine laboratory values can support differential diagnosis in individual cases to rule out hypothyroidism, nephrotic syndrome, or decompensated heart failure as an underlying or concomitant disease. The following parameters are available, among others: TSH, FT3, FT4 to rule out hypothyroidism; creatinine, GFR in serum and

total protein in collected urine to detect renal dysfunction or nephrotic syndrome, and NT-proBP to rule out decompensated heart failure.

2.2.8 Alternative diagnostic methods

In addition to classic imaging techniques, various devices have been used in lymphology and edema diagnostics for several years, based on the principle of quantifying the water balance of tissues by determining their electrical conductivity (known as bioimpedance measurement). None of the available data is based on evidence-based studies. A pilot study by Birkballe et al. (2014) using a handheld device to determine the tissue dielectric constant (TDC) showed that the method can be used to draw conclusions about the presence of untreated lymphedema, but did not provide any diagnostic criteria for differentiating between decongested lymphedema, lipedema, and the tissue of healthy subjects. No evaluated data are available on the effectiveness of alternative diagnostic methods such as the bioimpedance method and the determination of the tissue dielectric constant (TDC). Published data suggest that it is not possible to diagnose lipedema.

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3 Epidemiology

Anya Miller

There are no epidemiological studies that meet current diagnostic criteria. The data available to date are based on the following publications. Almost all publications cite studies or papers that are more than 10 years old.

The estimate of up to 11% from Földi's textbook from 2003 is frequently cited. This figure was later retracted in a letter to the Süddeutsche Zeitung newspaper for an article and is no longer mentioned in editions from 2012 onwards. (Berndt et al. 2019; Földi et al. 2003)

The clinical report by Child et al. (2010) continues to be frequently cited. Lipedema is defined as disproportionate fat distribution below the waist, pressure pain, and a tendency to develop hematomas.
Patients at the lymphology clinic at St. George's Hospital in London were examined between 1994 and 2009. The diagnosis was made by two specialists, and in positive cases, other family members were examined. Patients with obesity, primary or secondary lymphedema were excluded. A total of 330 family members of 67 patients were identified. Based on these data, a prevalence of 1:72,000 was estimated. These figures refer exclusively to the selected clientele of this clinic.

A third frequently cited study by Herpertz describes that 15% of the 933 patients admitted to a lymphological rehabilitation clinic between May 1995 and March 1996 had lipedema. He clearly distinguishes between painless fat tissue proliferation and symmetrical lipohypertrophy with bulging tissue and pain, which he then refers to as lipedema (Herpertz 1997).

In a 2008 study on sonomorphology, Marshall and Schwahn-Schreiber describe 8-17% of all female patients in a specialist angiology and phlebology practice as affected, including mild forms (Marshall and Schwahn-Schreiber 2008a). Fourteen women and one man were examined for this publication. In contrast to obesity, spontaneous and contact pain are listed for obese individuals. Nevertheless, painless lipohyperplasia is classified as an early stage of lipedema. Two female patients were in this early stage. The male patient's findings were described as lipedema-like.

An article on the differential diagnosis of lymphoedema, phlephlebitis and lipoedema was also published in 2008. The diagnostic criteria are cited according to Wienert et al. (2005) as a clinical syndrome characterized by orthostatic leg edema and an increase in subcutaneous adipose tissue, accompanied by a fat distribution disorder, particularly in the upper and lower legs (Marshall and Schwahn-Schreiber 2008b). The authors propose a definition as a disproportionate distribution disorder of sonomorphologically altered subcutaneous adipose tissue with an increased number of fat cells (lipohyperplasia). Based on earlier literature, they estimate the prevalence in the general population to be 8%. The findings for non-invasive diagnostic criteria for lymphoedema and lipoedema – also in distinction to phleboedema – were compiled from 100 patients. Further calculations on epidemiology are not presented. According to the authors themselves, the figures are estimates from a monocentric, selected patient population.

In a further study in 2011, these two authors also adopted the definition of the DGP guideline at that time (Wienert et al. 2005) with symmetrical subcutaneous fat tissue proliferation,

a tendency to orthostatic edema, a tendency to hematoma, and sensitivity to touch (Marshall and Schwahn-Schreiber 2011). They recommend dividing the condition into an early stage with painless lipedema and a late stage with painful lipedema. According to this, 39% of the 62 women examined had lipedema. However, this also includes patients with pure lipomatosis regionalis. Later stages are defined based on the increase in adipose tissue and are reported at 9.7%.

Fife et al. (2010) describe lipedema as diet-resistant pathological fat distribution, mostly below the waist. In the early stages, only the retromalleolar region may be affected. Further symptoms include a tendency to bruise and pain (painful dysesthesia). In the authors' clinic, 22.7% of 792 patients with lower limb lymphedema also had localized fat accumulation in the legs. In these cases, they diagnosed additional lipedema.

No further information on epidemiology is provided.

Monocentric epidemiological studies with diagnostic criteria of disproportionate fat distribution, pain, hematoma tendency, and edema increasing during the day were conducted by Rapprich (Rapprich et al. 2015). Studies of 815 female patients at a general practice who presented with a wide variety of illnesses between July 2011 and July 2012 resulted in a diagnosis of lipedema in 5%. Of 126 female patients who presented with leg pain, 32.5% were diagnosed with lipedema.

were diagnosed with lipedema.

Forner-Cordero et al. (2012) reported that, in a retrospective analysis, 18.8% of female patients between 2005 and 2012 suffered from lipedema. This is also a monocentric study from a single clinic.

In another prospective, non-interventional study, data was collected from patients who presented with lipedema in a hospital in Spain between 2012 and 2019 (Forner-Cordero et al. 2021). The study primarily focused on the clinical manifestations of lipedema. No epidemiological data were collected in this single-center study.

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4 Compression therapy for lipoedema

Eberhard Rabe

Recommendation 4.1

	Recommendation	Agreement
In cases of diagnosed lipedema, compression therapy **should** be used to reduce pain in the affected extremities.	↑↑	Strong consensus (100%)

Recommendation 4.2

	Recommendation	Agreement
Compression therapy for lipedema **can** initially **be carried out** using medical compression stockings (MCS), compression bandages (CB) and medically adapted compression systems (MACS). In long-term treatment, MCS **should** be preferred in routine cases.	↔ ↑	Strong consensus (100%)

Compression therapy (CT) is considered part of the standard treatment for lipedema (Rabe et al. 2021). In two surveys conducted in 2014 and 2020, compression therapy was the most common conservative treatment (Lipoedema UK 2014, Paling et al. 2020). CT can be administered using medical compression stockings (MCS), compression bandages (CB), and medical adaptive compression systems (MACS) (Rabe et al. 2021). Intermittent pneumatic compression (IPC) can also be used (Rabe et al. 2021). MCU consists of a stocking-shaped elastic knit fabric, while CC achieves its effectiveness through the application of elastic and/or non-elastic bandages. In individual cases, the application of CC may cause constriction, nerve damage, or blistering. Underpadding the KV with cotton wool, foam bandages, and/or pelottes prevents these undesirable side effects.

4.1 Mode of action

MKS and KV have elastic properties, so that continuous, defined pressure is exerted on the extremity.

Lipedema is primarily neither an edema disease nor a clinical picture with venous or lymphatic dysfunction. The subjective symptoms and, above all, pain are the main focus here. Inflammatory processes in the fatty tissue are being discussed. The primary goal of compression therapy for lipedema is to reduce pain and other subjective symptoms. There are no prospective, comparative, randomized studies on inflammation and pain reduction with compression in lipedema. However, Paling et al. were able to show in their survey that symptoms decreased with the frequency of compression therapy (Paling et al. 2020). In a recent randomized prospective pilot study, six patients with lipedema were randomized into a group with an exercise program alone and a group with

exercise program and compression therapy (KKl 2, flat knit) and followed up for 6 weeks (Czerwińska et al. 2023). Compared to the group without compression, a significant reduction in palpation pain and hematoma tendency was observed in the compression group. In addition, there was also a tendency for leg circumferences to either remain the same or decrease with exercise in compression, while they tended to increase without compression. These results suggest that compression therapy in combination with exercise could improve quality of life and reduce symptoms.

In the venous area, a significant reduction in pain in leg ulcers and a reduction in other symptoms were demonstrated (Beidler et al. 2008; Beidler et al. 2009; Moñux et al. 2021; Murphy et al. 2002; Tkaczyk et al. 2021). Beidler et al. were also able to demonstrate anti-inflammatory effects under compression therapy in leg ulcers (Beidler et al. 2008; Beidler et al. 2009). Murphy et al. were able to demonstrate a reduction in serum cytokines during ulcer healing and compression therapy (Murphy et al. 2002). In lipedema, the increasing filling of the extensive cutaneous vascular network and the accumulation of fluid in glycosaminoglycans (GAGs) during the course of the day may play a role in the feeling of swelling and heaviness. Compression therapy with flat-knit materials could counteract this filling (Moñux et al. 2021). However, there are no prospective studies on this issue. In addition, compression therapy can shape and model the disproportionate fatty tissue. A reduction in fatty tissue through compression therapy is not to be expected. Progression prevention through compression therapy has not been proven.

If lipedema occurs in combination with venous edema, lymphedema, or hydrostatic edema, compression therapy can also have a positive effect on edema formation (Rabe et al. 2021).

Recommendation 4.3

	Recommendation	Agreement
Compression therapy for lipedema **should be** aimed at reducing pain and other subjective symptoms. . When combined with edema of other origins, the associated edema formation and reduction are also favorably influenced. .	↑↑	Strong consensus (100%)

Recommendation 4.4

	Degree of recommendation	Consent
Patients **should** be informed that compression is not suitable for reducing fatty tissue.	↑↑	Strong consensus (100%)

The age of the patient and the condition of the skin, muscles, and connective tissue, as well as the shape of the legs or arms, also play a role in the selection of compression material.

The extent to which the compression garment resists the increasing circumference during movement, edema formation, or

change from a lying to a standing position, thereby contributing to an increase in pressure under the compression garment. This property of the compression material is referred to as stiffness (Partsch et al. 2016).

Recommendation 4.5

	Degree of recommendation	Agreement
When selecting and prescribing In addition to providing the necessary pressure, compression materials **should** also **be** the most suitable material for the individual patient , as the effectiveness of compression treatment depends on both the pressure and the material properties.	↑↑	Strong consensus (100%)

Due to the occasionally complex shape of the legs with large circumferential changes over a short distance and the possible associated obesity, there are limitations to the use of a one-piece MKS in terms of both manufacture and donability. In such cases, a multi-part treatment (e.g., using Bermuda shorts, leggings, and stocking elements) should be used. Since lipedema does not affect the feet and hands, treatment with leggings or compression sleeves without hand sections should also be considered. The prescription of compression therapy is a medical service. Since the selection of suitable materials, the technical requirements for production and donability, and patient acceptance play a major role in lipedema, close coordination between the prescriber, the supplier, and the patient is advisable.

Recommendation 4.6

	Degree of recommendation	Agreement
The selection of compression material or a multi-part treatment **should be made** in close consultation with the patient, physician, therapist, and supplier in order to improve adherence and effectiveness in close consultation between the patient, physician, therapist, and supplier.	↑↑	Strong consensus (100%)

4.2 Knit type of MKS

Medical compression stockings are manufactured in various knits (Rabe et al. 2021):

- ***Flat knitted with seam***, machine-formed, with at least one knitted and one inserted elastic thread in every second row of stitches. Due to the type of knitting, flat knitted MCS generally have a higher stiffness but also a higher bending stiffness than circular knitted MCS. The higher bending stiffness bridges deeper fabric folds better without causing constriction due to "slipping in." These properties **should** be used when treating patients with severe lipedema and accompanying obesity.
- ***Single and double circular knit***, seamless, machine-formed, with at least one knitted and one inserted elastic thread in every second row of stitches. Adjustment to the shape of the leg is only possible by changing the stitch size (fixed or

loose knit) or thread tension. For example, in cases of severe lipedema and in obese patients, there may be very large changes in circumference or deep tissue folds along the leg or arm that cannot be treated with circular knit MKS for technical reasons.

Recommendation 4.7

	Recommendation	Agreement
Lipedema **can** generally be treated with round or flat knitted MKS. For large circumferential changes to a limb or conical limbs, as well as for deep tissue folds, a flat knit quality should be prescribed, as round knit material is unsuitable for these anatomical conditions. tissue folds, flat-knit stockings **should** be prescribed, as circular-knit material is unsuitable for these anatomical conditions.	↔	Strong consensus (100%)

Recommendation 4.8

	Degree of recommendation	Agreement
Due to the knitting method, flat-knit MKS generally exhibit higher stiffness but also higher bending stiffness. These properties **should** be utilized when treating patients with lipedema and accompanying obesity. . The higher bending stiffness bridges deeper tissue folds better without causing constriction by "slipping in."	↑	Strong consensus (100%)

4.3 Compression pressure

The MKS compression classes (KKL) I, II, III, and IV differ from each other in the intensity of the pressure exerted on the limb at rest. The KKL are standardized based on the pressure at rest in the fetlock area. However, it is not only the resting pressure that is important for the effectiveness of MKS, but also the working pressure and thus the material, which differs in terms of elasticity and stiffness. Higher working pressure can be achieved both through higher resting pressure and through higher stiffness. For this reason, medical compression stockings made of different materials are available in the various KKL classes.

Recommendation 4.9

	Degree of recommendation	Agreement
The type of stocking and strength of the required pressure, i.e.**,** the CKL**, should** be adapted to the location, clinical findings, and severity of the symptoms and changes. . A rigid assignment of a KKL to the diagnosis of lipedema **should**	↑↑ ↑↑	Strong consensus (100%)

, as the aim of compression therapy is to improve subjective symptoms, especially pain.		

Recommendation 4.10

	Recommendation	Agreement
The lowest KKL that leads to sufficient symptom relief **should** always be preferred. This supports adherence to compression therapy.	↑↑	Consensus (89.5%), Consensus without IK (86.7%)

4.4 Side effects and risks

Recommendation 4.11

	Recommendation	Agreement
To avoid side effects and risks of compression therapy**,** the rules for proper This includes padding areas at risk of pressure and regular skin care.	↑↑	Strong consensus (100%)

For information on risks and side effects, please refer to the guideline Medical Compression Therapy of the Extremities with Medical Compression Stockings (MCS), Phlebological Compression Bandages (PCB), and Medical Adaptive Compression Systems (MACS) (Rabe et al. 2021).

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5 Lipedema and IPK

Stefanie Reich-Schupke

Recommendation 5.1 in analogy to the IPK guideline (Schwahn-Schreiber et al. 2018)

	Strength	Agreement
IPK **should** be used to treat lipoedema in order to relieve pain and reduce accompanying oedema of other causes – including as a home therapy.	↑	Consensus (94.4%), Consensus without IK (94.1%)

The data on the use of intermittent pneumatic compression therapy (IPC) for lipedema is very limited. A Medline search (September 30, 2020) using the search terms
"lipedema" and "IPC" (1) or "pneumatic compression" (10) or "intermittent compression" (7) yielded only a few overlapping hits. The available data refer exclusively to the use of IPC on the legs.

In everyday clinical practice, IPK is used as a supportive measure within the framework of CPT, but not as a substitute for manual lymphatic drainage or compression therapy (Fetzer 2016; Herpertz 1997; Mendoza and Amsler 2019; Schwahn-Schreiber et al. 2018). Both from everyday clinical experience and in case series, it has been shown to be effective in reducing edema, pain, and capillary fragility (Svensson et al. 1993; Szolnoky et al. 2008a; Szolnoky et al. 2008b). The device settings must be selected on an individual basis and adjusted to the patient's pain sensitivity. Multi-stage full-leg or pant cuffs have proven effective for treating the legs. It is important to ensure that they fit accurately.

There is only one prospective, randomized pilot study evaluating CPT in the treatment of lipedema, which demonstrated a reduction in limb volume with improvement in pain symptoms in a small number of cases. Additional IPK with empirical device adjustment did not result in any further volume improvement, but can save costs by reducing the time required for manual lymphatic drainage and is considered safe (Szolnoky et al. 2008a). Szolnoky also demonstrated a reduction in capillary fragility with CPT and IPT (Szolnoky et al. 2008b; Szolnoky et al. 2011).

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6 Drug therapy

Markus Stücker, Gabriele Faerber

Recommendation 6.1

	Degree of recommendation	Agreement
Diuretics **should** not be used to treat lipedema. The use of diuretics in lipedema patients for internal medical reasons is possible.	↑↑	Consensus (94.4%)

The main goals of lipedema treatment are to reduce symptoms, improve functional limitations, and prevent the disease from getting worse (Buso et al. 2019). Drug therapy is not considered important (Gensior and Cornely 2019), as evidenced by the fact that it is not mentioned in any recent reviews (Kruppa et al. 2020) and that no systematically collected data on drug therapy are available (Buso et al. 2019). In principle, beta-adrenergic agonists, corticosteroids, flavonoids, and selenium are considered in reviews, but no detailed recommendations on indications or dosage are given (Buck and Herbst 2016). Treatment with diuretics is viewed critically. As with idiopathic edema or fluid retention syndrome, which can also occur in combination with lipedema in approximately 10% of cases (Pereira de Godoy and Guerreiro Godoy 2022), long-term abuse of diuretics can worsen edema symptoms through counterregulation or even cause them in the first place. The reduction in plasma volume can lead to potassium deficiency, renal salt and water retention, and secondary aldosteronism (Ely et al. 2006; Kuchel and Ethier 1998; Veluri and Badwal 2019).

Recommendation 6.2

	Level of recommendation	Agreement
In the initial phase of treatment or if the condition worsens significantly, pain therapy with medication **may be considered.** However, according to expert experience, this is usually ineffective in lipedema.	↔	Consensus (88.8%)

Pain is an integral part of the clinical picture of lipedema (Schmeller and Meier-Vollrath 2008).

There are no studies on the effectiveness of medication-based pain therapy in patients with lipedema. Inflammation and hypoxia are assumed to be the causes of the pain.

Recommendation 6.3

	Level of recommendation	Agreement
Prescriptions for medications associated with weight gain and/or edema formation **should be made** with risk	↑	consensus (88.8%)

benefit assessment.		

In patients with lipedema, weight gain leads to an increase in adipose tissue in the extremities and, in most cases, to an exacerbation of symptoms (Frambach et al. 2016). Medications such as certain antidepressants, thiazolidinediones, and glitazones (e.g., rosiglitazone) should be considered here.

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7 Physiotherapy for lipedema

Constance Daubert

7.1 Treatment options for the main symptom of pain

Recommendation 7.1

	Recommendation	Agreement
If compression is not applicable in individual cases or does not lead to pain reduction on its own, the leading symptom of pain **can** be treated with additional lymphatic drainage in combination with other therapeutic techniques Manual lymphatic drainage is not aimed at reducing volume, but at modulating the C fibers.	↔	Strong consensus (100%)

Recommendation 7.2

	Level of recommendation	Agreement
Since exercise in compression or an exercise program is an important element in pain reduction, it **should** be included in the overall therapeutic concept.	↑↑	Strong consensus (100%)

Recommendation 7.3

	Degree of recommendation	Agreement
The vibration plate **can** be used to increase the pressure pain threshold.	↔	Strong consensus (100%)

7.1.1 Manual lymphatic drainage

There is no evidence to support the use of manual lymphatic drainage (MLD) as a standalone therapy for lipedema. Rather, it has been investigated in various combinations with other forms of therapy. Nevertheless, it should be noted that manual lymphatic drainage has both a sympatholytic effect (Brenke and Seewald 1992; Do et al. 2015; Hutzschenreuter and Ehlers 1986; Kim 2014) and an increase in pain tolerance and 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 pelvis during manual lymphatic drainage (deep abdominal drainage) leads to an increase in vagal activity and may have an anti-inflammatory effect.

According to a three-arm intervention study by Antoniak et al. (2022; n = 30), manual lymphatic drainage in overweight patients significantly reduced both the 2-hour post-load glucose level (2h PG) (p= 0.050) and C-reactive protein (p= 0.041). In

the group of severely overweight patients, HbA1c decreased significantly after MLD (p= 0.013).

This study also found a reduction in insulin levels in overweight patients, although the results were not significant.

Since a very low insulin level is sufficient for local lipogenesis in lipedema, this could be a possible therapeutic approach. However, there is no study on insulin levels and lymphatic drainage in lipedema patients.

7.1.2 Manual lymphatic drainage in combination with other therapeutic techniques

Atan and Bahar-Ozdemir (2021) demonstrated a benefit of complex physical decongestive therapy (CPT) + Exercise program group compared to the groups receiving intermittent compression therapy (IPK) + exercise program and the group receiving only the exercise program. Significant improvements were achieved in pain reduction ($p = 0.045$) and volume reduction ($p = 0.017$ right leg; $p < 0.001$ left leg). The physical functioning subscore of the SF-36 (QoL) also showed significant results ($p = 0.040$). The study included lipedema patients with type 3 lipedema and stages 3 (30%) and 4 (70% - lipedema plus lymphedema).

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

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

All groups received the same exercise program consisting of: warm-up; flexibility exercises; aerobic training on the treadmill, strengthening exercises, and a cool-down for a total of 60 minutes.

Szolnoky et al. (2011) demonstrated a significant ($p = 0.0001$) reduction in pain (Pain Rating Scale) through CPT in a two-arm RCT with 38 lipoedema patients. The intervention group (n=19) received MLD, IPK, skin care, bandaging and exercise in compression over five days. The control group (n=19) received skin care only.

7.1.3 Vibration plate

To increase the pressure pain threshold (dolorimeter measurement), Schwarze (2012) found that the use of a vibration plate (Galileo) in a total of n= 38 patients was significantly positive after a six-week intervention (increase in pressure pain threshold of 0.70 kg/cm²). In the two-arm RCT (group 1 Galileo n = 21 / group 2 leg training n = 17) over a total period of 12 weeks, participants received either leg training on the vibration plate twice a week (45 minutes each) for six weeks in the clinic and then six weeks of home-based leg training, or in group 2, solid leg training for six weeks in the clinic and then six weeks of home-based leg training. The leg training group (group 2) also achieved a significant increase in the pressure pain threshold, but only after 12 weeks.

Neither group showed any significant changes in leg volume.

7.1.4 Aerobic training, stretching, moderate strength training

Schwarze (2012) achieved pain reduction through leg muscle training after 12 weeks. The leg muscle training included ten exercises (aerobic training/strength training), which were performed 2-3 times a week over a period of 12 weeks. An increase in volume was observed during the training.

Atan and Bahar-Ozdemir (2021) (see above) also conducted a 60-minute training session in their three-arm study. This consisted of a warm-up, stretching, aerobic training on the treadmill, strength training, and a cool-down. ==The group that performed only the described training achieved significant results in terms of pain reduction ($p = 0.002$) and volume reduction (right leg; $p = 0.028$ / left leg; $p = 0.023$). However, when comparing the three groups with each other, the exercise group achieved the worst results.

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

Kronimus et al. (2020) published the results of three individual cases (n = 3) in a pilot study. Pain reduction and an improvement in quality of life (SF-36) were observed in the context of a ten-week aquacycling therapy program. The patients participated in a 45-minute intervention once a week. The severity of lipoedema was not specified.

Exercise in water causes an increase in atrial natriuretic peptide (ANP, Weiß et al. 2003; Wenzel and Muth 2002), which contributes to water regulation in the body by promoting the excretion of water and salt via the kidneys and also promotes ketone formation (Birkenfeld et al. 2005; Schnizer et al. 2006). According to the research team led by Birkenfeld in 2005, ketone formation promotes lipolysis (Birkenfeld et al. 2005). However, the study results do not show any superiority of exercise programs over other techniques for pain reduction.

Van Esch-Smeenge et al. (2017) already found in 2013 that the strength of the quadriceps femoris muscle is reduced in lipedema patients (n = 22). Hodson and Eaton (2013) also pointed out in their study that there is a misalignment of the hip joints and/or knee joints in patients with lipedema syndrome. According to the authors, the misalignment is directly related to hypermobility of the tissue, which is caused in part by a low number of elastic fibers, i.e., fibers that can spring back. The misalignment subsequently affects gait, which in turn can lead to orthopedic damage, primarily to the hip and knee joints (Volkan-Yazici et al. 2021).

Furthermore, although there are no studies linking it to lipedema, it should be mentioned that interleukin-6 (IL-6) is released during exercise, especially after long periods of exercise lasting more than an hour (Fischer 2006). IL-6 promotes lipolysis and also has anti-inflammatory effects.

Furthermore, Krüger (2017) demonstrated in a review that exercise reduces inflammation (MCP-1; TLR 1; TLR 2; TLR4, IL-10, Il-1RA) in adipose tissue. According to the author, this also reduces systemic inflammatory processes.

Wegner et al. (2014) further demonstrated that exercise alleviates depressive episodes.

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

Several studies have pointed to a significant improvement in existing 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). In a review by Eriksson and Gard (2011), physical activity was considered effective in reducing depressive moods (see also Chapter 8).

In a recent study by Michalak et al. (2022), a significant correlation (p<0.01) between increased stiffness of the myofascial system and depression was identified. Among other things, the authors point to the link between elevated levels of the cytokine TGF-ß 1 and increased myofascial stiffness. TGF-ß 1 is relevant in stress-related dysregulation of the autonomic nervous system, among other things. A total of 80 people participated in this study, with 40 participants suffering from depression and 40 participants serving as a control group without depression. The stiffness and elasticity of the fasciae were measured using the electronic tissue compliance meter (ETCM). Mobilization of the myofascial system using a foam roll led to an improvement in the depressive status of 69 participants with depression. The authors used the Assessment Memory Bias to evaluate the condition of the participants. The participants were randomized into an intervention group (n=38) or a placebo group (n=31).

7.1.5 Moderate massage therapy

According to Field (2014) and Field et al. (2002), moderate massage leads to an improvement in the deep sleep phase. According to Field, this in turn reduces the release of substance P, which leads to a reduction in pain. The concentration of substance P was measured in the saliva of patients with fibromyalgia.

In other pain syndromes (burns, juvenile rheumatoid arthritis, migraine), moderate massage techniques were found to reduce cortisol levels in conjunction with an increase in serotonin and dopamine in saliva and urine samples (Field et al. 2005; Field et al. 1997; Field et al. 1998; Hernandez-Reif et al. 1998).

Comparative studies on lipoedema are lacking. A possible transfer of the above findings on the effects of moderate massage therapy should be carried out.

Internationally, there is experience with various massage techniques that have shown a alleviating effect on the symptomatic effect on pain in studies with a small number of cases (SAT/subcutaneous fat cell therapy, Herbst et al. 2017). No recommendation can be derived from this.

7.2 Treatment options for lipedema with additional edema of other origins with the aim of reducing edema

Recommendation 7.4

	Recommendation	Agreement
Complex physical decongestive therapy **should** be used for lipedema with additional edema of other origins.	↑	Strong consensus (100%)

Recommendation

	Degree of recommendation	Approval
The additional practice of aqua sports (e.g., aqua cycling) **can** have a positive effect.	↔	Strong consensus (100%)

7.2.1 KPE plus IPK

Volkan-Yazici and Esmer (2022) demonstrated in a recent study using the Perometer (400 NT) in 14 lipoedema patients (affecting the upper extremities) a significant reduction in the circumference of both arms at three of four measurement points (p-values of the measurement points < 0.05). Significant results were also obtained after daily therapy (5 days per week for 3.5–5.5 weeks) with regard to arm volume (left p = 0.023; right p = 0.041).

The patients received 45 minutes of MLD; 30 minutes of IPK; skin care and exercise in bandages. Since the hands were not affected, bandaging only began at the wrist. After the intervention, the patients wore the custom-made compression stockings until the next day.

Volkan-Yazici et al. (2021) showed in a second study a significant reduction in leg volume in lipedema patients (n= 23; p< 0.05) after five to six weeks of KPE plus IPK. Here, too, measurements were taken using the Perometer. According to Murat Esmer (author), the therapy was administered to patients with varying degrees of severity. MLD was performed for 45 minutes, followed by 30 minutes of IPK. The patients were also bandaged.

The study published by Szolnoky et al. in 2008 recorded a significant reduction in volume (p<0.05) in two randomised groups of 24 participants (Szolnoky et al. 2008a).
A group treated with CPT (n = 11) (MLD 60 minutes, bandaging, skin care, exercise in compression) was compared with a group in which IPK was added as an additional therapy unit (n = 13; MLD 30 minutes, IPK 30 minutes, bandaging, skin care, exercise in compression).

The IPK used in addition to CPT did not show any significant advantage.

7.2.2 CPT vs. aquacycling

Becker et al. (2018) investigated the effect of aquacycling (AC) in n= 10 lipedema patients (2 lipedema, 8 lipedema with additional lymphedema) over a period of ten weeks. Five patients were randomized to the control group with MLD alone (1-2 times/week). The

The intervention group received additional aquacycling once a week. No significant reduction in volume was observed in either group. In a direct comparison between the groups, a reduction in volume was observed in the intervention group (plus AC) [266.37 cc (SD 435.60)]. According to Becker et al., the MLD group showed an increase in volume [439.95 cc (SD 1246.90)].

7.2.3 Galileo (vibration plate) / leg training

In the study by Schwarze (2012) described above, neither the group treated with the Galileo vibration plate nor the leg training group showed a reduction in volume. Instead, the author observed an increase in volume in the leg training group without vibration plate, albeit not significant.

7.3 Therapy options of lipedema for reducing hypertrophic tissue

7.3.1 Shock wave therapy (SWT)

Siems et al. (2005) demonstrated an antihypertrophic effect in the treatment of 26 lipedema patients using shock wave therapy (SWT). This was determined based on plasma MDA (malondialdehyde) and plasma protein carbonyl concentrations and compared with plasma data from 80 unaffected individuals.

The intervention was divided into two groups, with group 1 receiving CPT+ ly with SWT and group 2 receiving SWT alone.

Group 1 showed more pronounced effects. No possible significance was demonstrated.

7.3.2 Manual subcutaneous fat cell therapy (SAT)

In a study by Herbst et al. (2017), an improvement in tissue structure in the sense of an antifibrotic effect was demonstrated in seven female patients.

7.4 Therapy option for improvement the quality of life (QoL) of lipedema patients

Recommendation 7.6

	Recommendation	Agreement
Manual lymphatic drainage in combination with other therapeutic techniques **should** be considered to improve quality of life (QoL).	↑	Consensus (94.4%)

Three studies investigated the effect of therapy techniques on the quality of life of lipedema patients (Atan and Bahar-Ozdemir 2021; Donahue et al. 2021; Kronimus et al. 2020). Despite the relatively small number of participants (n= 7 Donahue et al./ n= 3 Kronimus et al.), a positive effect of manual lymphatic drainage in combination with other therapeutic techniques was demonstrated in lipedema patients in stages 3 and 4 (Atan and Bahar-Ozdemir 2021) as well as in lipedema patients in stages 1 and 2 (Donahue et al. 2021).

Aquacycling showed an improvement in quality of life in two out of three cases in the study by Kronimus et al. (2020).

Schleip and Jäger (2014) pointed out a correlation between psychosomatic illnesses and altered interoceptive signal transmission in myofascial systems. More recent studies support this statement (Michalak et al. 2022). According to the authors, interoceptive signaling is significantly increased in anxiety disorders and depression. Studies on lipedema patients are lacking.

7.4.1 Therapy option for reducing elevated sodium levels in lipedema tissue

Donahue et al. (2021) found a significant reduction in sodium levels ($p = 0.005$) in seven patients, which was demonstrated using 3-Tesla sodium and water magnetic resonance imaging (MRI). An increase in sodium content in the tissue of lipedema patients was postulated by Crescenzi et al. (2018) and Crescenzi et al. (2020).

7.5 Physiotherapy research approaches

7.5.1 Therapy option for reducing capillary fragility in lipedema

Szolnoky et al. (2008b) demonstrated ($n = 38$) a significant reduction ($p < 0.001$) in capillary fragility through CPT plus IPK. The 21 patients received MLD for 30 minutes, IPK for 30 minutes (30 mmHg), bandaging, skin care, and exercise in compression (walking: twice daily for 30 minutes) over the course of a five-day study. The control group ($n = 17$) was treated with skin care.

Compared to another control group ($n= 10$), lipoedema patients had a significantly increased number of petechiae ($p<0.05$).

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8 Psychosocial therapy

Gabriele Erbacher

8.1 Lipedema and psychosocial stress

Recommendation 8.1

	Recommendation	Agreement
According to the biopsychosocial concept, the diagnosis of lipedema-associated pain **should** take into account not only medical factors but also psychosocial factors.	↑↑	Strong consensus (100%)

Recommendation 8.2

	Degree of recommendation	Agreement
Mental disorders can influence the symptoms and quality of life of lipedema patients and **should** be taken into account in the diagnosis and treatment of lipedema. These include, for example, eating disorders, depression, and post-traumatic symptoms following violence and abuse. An interdisciplinary therapeutic approach should be pursued.	↑	Strong consensus (100%)

Women diagnosed with lipedema can suffer from numerous psychosocial stresses; the vast majority of patients also exhibit mental disorders such as 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 lipedema from various countries show significantly higher physical, emotional, and social impairments in women with lipedema compared to women in the general population (Dudek et al. 2016; Dudek et al. 2018; Romeijn et al. 2018).

The proportion of mental disorders and their intensity can vary significantly depending on the outpatient or clinical setting.

In a single-arm retrospective, single-center cohort study conducted at a lymphology clinic with 150 patients with a confirmed diagnosis of lipedema, 46.7% of women reported pain-related disorders such as mild to moderate depression, anxiety disorders, eating disorders, or post-traumatic stress disorder. In addition, 33.3% of the women examined showed psychological abnormalities such as psychophysical exhaustion syndrome or burnout (Erbacher and Bertsch 2020; Maslach et al. 1997).

The study results of Frambach et al. (2015) show that the dimension of "mental health" is even more severely impaired in women with lipedema than the dimension of
'physical health', as measured by the internationally recognised quality of life instrument SF 36 (Bullinger and Kirchberger 1998).

In a cross-sectional study of 26 patients with medically confirmed lipedema and a healthy control group of 26 subjects of the same age, the severity of emotion regulation (measured using the Difficulties in Emotion Regulation Scale (DERS)) and anxiety (measured using the Hamilton Anxiety Scale (HAM-A) (Al-Wardat et al. 2022). The lipoedema patients reported considerable difficulties with emotion regulation in the questionnaire (scales: impulse control, goal-directed behavior, emotional awareness, emotional clarity, non-acceptance of emotional reactions, and emotion regulation strategies) and more severe anxiety symptoms than patients without lipedema. The authors therefore recommend that more attention be paid to emotion regulation and mental health in lipedema patients.

However, previous studies suggest that psychological stress and disorders are a consequence of lipedema and that lipedema is responsible for these psychological symptoms. Current data, which examined both symptoms (lipedema-associated pain and psychosocial stress) separately and placed them in a temporal context, indicate that in 80% of patients, the psychological stress was already present in the 12-month period prior to the onset of soft tissue pain and thus also prior to the development of lipedema (Erbacher and Bertsch 2020).

These data therefore indicate that lipedema is not the cause of the psychological symptoms.

Similarly, a review of lipedema examines the influence of mental health on both the development of initial symptoms of lipedema and the severity of the symptoms experienced (Czerwinska et al. 2021). The authors conclude that mental disorders increase the experience of pain in lipedema.

8.2 Obesity and psychosocial stress

The vast majority of women diagnosed with lipedema suffer from another condition: obesity. Data from several European centers that treat lipedema patients show that after BMI classification (which, in connection with lipedema, should be considered problematic (see Chapter 2) , up to 80% or more of patients are obese (BMI$\geq$ 30 kg/m^{2}), and approximately 50% of these are even morbidly obese (BMI$\geq$ 40 kg/m^{2})(Child et al. 2010; Dudek et al. 2018; Erbacher and Bertsch 2020). It is particularly important to address obesity in women with lipedema, as coincidental obesity is an aggravating factor for lipedema.

Obesity is also an independent risk factor for the development of mental disorders (Luppino et al. 2010; Sikorski et al. 2015).

A large sample of 495 normal-weight, 1,550 overweight, and 910 obese people from the general population and from rehabilitation clinics shows that obese people have significantly more mental disorders such as depression, anxiety, or somatoform disorders (OR 2.0 and 1.4, respectively) than normal-weight people (Baumeister and Harter 2007).

At the same time, the usually coincidental occurrence of lipedema and obesity can lead to increasing mobility problems. According to recent data, the perceived limitation of mobility alone represents a significantly increased risk of developing depression (Linsmayer et al. 2019).

A meta-analysis of prospective studies highlights the bidirectional relationship between depression and obesity: obesity increases the risk of developing depression by 55%, while the presence of depression increases the risk of obesity by as much as 58% (Luppino et al. 2010).

The disproportionate distribution of fat tissue in the legs (and sometimes the arms) can lead to difficulties in accepting one's own body and to stigmatization, especially against the backdrop of the current beauty ideal of slim and thin legs, which is prevalent among many women affected by lipedema (Dudek 2017; Fetzer 2016; Nath 2019).

In addition, the higher the proven media consumption of women and girls, the greater their dissatisfaction with their own bodies (Swami et al. 2010). The beauty ideal of female adolescents is already below the normal weight for their age group (Schuck et al. 2018). In vulnerable adolescents and women, this can create social pressure that leads to a spiral of dieting, which in turn regularly leads to further weight gain (Bertsch and Erbacher 2018b; Mann et al. 2007; Pietilainen et al. 2012).

8.3 Mental stress and chronic pain

In numerous "pain disorders," a connection between psychological stress and pain perception has already been well documented (Baerwald et al. 2019; Bischoff et al. 2016; Linsmayer et al. 2019; Tegethoff et al. 2015; Viana et al. 2018).
A chronic physical symptom, such as pain, fatigue, or dizziness, that leads to significant functional limitations in important areas of life (work, family, leisure) can then be diagnosed as a somatic stress disorder and treated on an interdisciplinary basis. For women with lipedema and limitations in important areas of life, this means that their pain is taken seriously as a combination of physical and psychological factors.
The current state of research on the influence of psychological factors on pain experience and the risk of chronicity is very consistent. There is solid scientific evidence that the following factors can 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):

- Catastrophizing thoughts
- Anxiety (especially illness-related fears)
- Passive pain behavior (protective behavior and avoidance of movement for fear of renewed pain) (fear avoidance model)
- Loss of control
- Depression, helplessness, and hopelessness
- Distress (negative stress)
- Focusing attention on the pain and
- the expectation of increased pain
- Violence/sexual abuse (Erbacher and Bertsch 2020; McLaughlin et al. 2016)

The information provided to the patient about the disease plays a major role in these factors in particular (Dudek et al. 2016; Erbacher and Bertsch 2020).
The consequences of misinformation can include not only an increase in catastrophic thoughts and anxiety (e.g., fear of disease progression) (Bertsch and Erbacher 2018a), but also a disruption of the doctor-patient relationship (Mendoza 2020).

Experiences of physical violence and/or sexual abuse also play an important role in lipedema. According to a study of 150 patients with a confirmed diagnosis of lipedema, 52% reported such a background (Erbacher and Bertsch 2020). The patients also showed correlations between mental disorders such as depression or post-traumatic stress disorder and the maximum and minimum pain levels they experienced in everyday life (Erbacher and Bertsch 2020). 52% reported having experienced physical violence or sexual abuse in the past, which is significantly higher than the figures for the general population (Erbacher and Bertsch 2020).

A prospective study also confirms this aspect for other types of chronic pain: childhood violence that subsequently led to a mental disorder predicts later pain conditions (McLaughlin et al. 2016). The decisive factor here is the inability to cope with the experience, rather than the event itself.

In addition to the pain-modulating factors mentioned above, chronic stress also plays a central role in the perception of pain. Due to the strong neurobiological overlap between the stress and pain processing systems, pain can also be generated purely centrally. This is then referred to as "stress-induced hyperalgesia" (SIH) (Egloff et al. 2016).

8.4 Patient education and psychosocial therapy approaches

From the pain-intensifying factors described in Chapter 8.3, it is possible to derive those factors that can lead to pain relief (Klinger 2017):

- Decatastrophization
- Reducing fear of pain through movement
- Conveying a sense of control and security in relation to the pain and its progression
- Treatment of (pain-associated) depression
- Focusing attention away from pain and toward other aspects of life that improve quality of life
- Expectation of pain relief

Research shows that reducing catastrophic thoughts and developing helpful thoughts when dealing with pain is an important influencing factor that also leads to long-term stabilization of therapy results (Christiansen et al. 2015).

The approaches of Pain Neuroscience Education (Louw et al. 2016; Moseley and Butler 2015a; Moseley and Butler 2015b), cognitive behavioral therapy (CBT) (Probst et al. 2019), acceptance and commitment therapy (Sturgeon 2014), or EMDR (Gerhardt et al. 2016) can be helpful.

While cognitive behavioral therapy aims to break the vicious circle of fear avoidance (Liedl and Knaevelsrud 2008), the mindfulness-based approach of acceptance and commitment therapy enables an increase in psychological flexibility. Both therapeutic approaches have been shown to have a positive influence on pain intensity and improvements in depression and quality of life (Hughes et al. 2017; Veehof et al. 2016).

The factors described above that contribute to pain relief should be integrated into approaches that include patient education and the promotion of self-management (cf.
Chapter 9). Providing evidence-based information and setting realistic expectations regarding improvement of symptoms is of central importance.

realistic expectations regarding the improvement of symptoms is of central importance.

In the spirit of "good psychotherapy" (Gerger et al. 2020), it is important to involve the patient in decision-making processes and to encourage her to play an active role in improving her quality of life.

8.5 Screening for relevant and common psychological stressors, in accordance with the recommendations of other guidelines

Recommendations for screening are listed in the appendix.

Recommendation 8.3

	Recommendation	Agreement
Serious mental illnesses (e.g., severe eating disorders or severe depression) **should** be treated before surgical procedures.	↑↑	Consensus (94.4%)

8.6 References

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9 Self-management

Gabriele Erbacher, Susanne Helmbrecht

Recommendation 9.1

	Recommendation	Agreement
Effective self-management is an important component of health literacy. It **should** be promoted and patients should be encouraged to take an active role. Problem-solving strategies and specific individual therapy goals **should** be developed together to promote increased self-efficacy.	⇑⇑ ⇑⇑	Consensus (88.8%)

Recommendation 9.2

	Recommendation rating	Agreement
Self-management **should** be supported by appropriate measures taken by the treating professionals, with responsibility remaining with the patient. Practitioners **should** reinforce successes positively. Confrontational behavior **should** 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 those affected to take control of their personal lives and development. This includes sub-skills such as motivation, goal setting, planning, time management, organization, success monitoring, and feedback (Seidel et al. 2019).

People with chronic illnesses should be empowered to cope well with their condition. This includes setting their own goals and being able to communicate effectively with healthcare professionals, family members, and friends about their illness, goals, and needs (Dierks 2019).

Self-management is distinguished from similar terms such as health literacy and empowerment. While self-management is an individual-centered concept aimed at coping with illness (Dierks 2018), political empowerment as a concept focuses on participation, empowerment, and change.

Originally, the healthcare sector primarily used information transfer, which tended to be didactic, without involving self-management. The basic assumption behind this approach was that only the direct provision of disease-specific information by an expert would lead to behavioral change, which would then improve clinical outcomes. However, this is too simplistic. Several reviews of randomized controlled trials show that the

providing patient-relevant information—without incorporating self-management strategies—is not very effective (Gibson et al. 2002; Norris et al. 2001).

According to current findings, patient education based on evidence-based information and self-management must go hand in hand.

Providing scientifically sound information about the disease as part of patient education is also essential in the case of lipedema. Successful self-management can only be established on the basis of valid information. Misinformation prevents successful self-management and can lead to a worsening of the disease (Mendoza 2020).

Current self-management approaches assume that teaching problem-solving strategies for dealing with the disease and increasing self-efficacy (confidence in one's own ability to overcome challenges through one's own actions) are central to achieving long-term clinically relevant improvements (Bodenheimer et al. 2002).

For lipedema, this could mean that patient education and self-management go hand in hand and that, alongside the healthcare professional, the woman affected by lipedema herself is the person who has the greatest influence on the success of treatment.

9.2 Promoting self-management

Self-management can be promoted in two ways: directly through measures (e.g., self-management courses) for the patient, and indirectly through supportive appreciation from healthcare providers (doctors, therapists from various professional groups).

On the part of the healthcare professional, self-management can be promoted through the following measures:

1. Building relationships, gaining trust
2. Listening and making appreciative comments enhance the patient's resources
3. Addressing unfavorable influences and valuing efforts
4. Support those affected with specific techniques:
   Ask open questions, reflect, acknowledge, summarize, provide information (ask for permission, provide information, ask follow-up questions).
5. Provide or recommend information brochures, websites, and magazines for further reading

First, clarify the extent to which the patient is capable of self-management. If there are limitations, ask whether support from others is needed and organize this:

For example, is there a supportive partner, family, self-help group, or network available?

Limitations in the ability to self-manage arise in some people—particularly in lipedema patients (Erbacher and Bertsch 2020)—with mental disorders such as depression (Egede 2005; Reinecker and Siegl 2004). In such cases, self-management is often significantly impeded by the mental disorder and should not be confused with a lack of willpower or motivation. These patients may require closer support during certain phases or referral to other specialist groups, such as psychotherapists.

On the patient's side, self-management can be promoted through the following measures:

1. Training in problem-solving strategies (defining the relevant problems, obtaining relevant information, weighing up different possible solutions, deciding on a solution, implementation, and evaluation (reviewing the results)
2. Learning to make decisions (applying the knowledge gained to everyday situations)
3. Increasing self-efficacy: (learning to recognize and utilize one's own resources)

As part of rehabilitation, the training modules for promoting self-management in medical rehabilitation (SelMa) (Meng et al. 2019) include the following modules:

1. Setting goals (What am I aiming for? What would I like to change at home?)
2. Planning (How do I do this in concrete terms?)
3. Overcoming, checking, and rewarding obstacles (What could go wrong? What could I do then? How do I check whether it works?)
4. Checking and rewarding

Special self-management programs can support successful self-management in patients with chronic diseases. Health experts promote self-management through behavior-oriented counseling and motivational conversations on an equal footing (Miller and Rollnick 2015). The goal should be for the patient to become an expert on their own disease.

First and foremost, everyday life must be adapted to the requirements of the disease, even if this means changing one's lifestyle. Developing new, health-promoting habits takes between 18 and 254 days and should not be underestimated in terms of the challenge it presents (Lally et al. 2010).

The so-called 5A strategy of health counseling can be used as a form of guidance for self-management.

A key component of any intervention to promote self-management in the health sector is a cooperative relationship between health experts (doctors, therapists from various professional groups) and patients.

In the 5A strategy for health counseling, which has already been used successfully in obesity counseling, the practitioner takes into account both the patient's psychological situation and, above all, their motivation (Vallis et al. 2013). The counseling takes place in five steps:

Ask (inquire), **Assess** (assess expectations, behavior, and progress), **Advise** (provide advice),
Agree (agree), **Assist** (support)

Interventions to promote self-management are generally aimed at behavioral change. Motivation and confidence in one's own abilities are crucial for maintaining new behaviors.

Behavioral change in the sense of the self-management approach can only be successful if the person affected has good reasons for changing their current situation. From the perspective of the lipedema patient, the benefits of the behavioral change must clearly outweigh the effort involved. The likelihood that the patient will actually achieve their goals is higher if they set the goals themselves (Dolatschek 2002).

Appreciative support enables the practitioner to promote increased motivation and the attainment of an active expert role in the patient. The willingness of women with lipedema to take on this expert role is evident in their participation in self-help groups or internet portals. Motivation and confidence are the essential foundations for behavioral change.

Targeted questions can be used to intervene, especially in cases of low self-efficacy or low importance of the health goal.

When a patient says that a health issue is not very important to her, practitioners often respond with reproaches.

People are far more likely to change their cherished habits if they are convinced themselves and do not feel they have their backs against the wall and have to defend their vices or bad habits. Giving up habits is more difficult than learning new behaviors.

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

Patients often fail because of their own excessive expectations of themselves (Miller and Rollnick 2015).

Behavior that is detrimental to health (such as binge eating when stressed) serves a neurobiological purpose in regulating stress. In the short term, this reduces stress levels, which the brain perceives as a reward.

9.3 Self-management programs and their effectiveness

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

The promotion of self-management (e.g., in guided or self-help groups) could be based on generally effective programs for promoting self-management.

The effectiveness of self-management has been investigated and confirmed for various chronic diseases and a wide range of services (Taylor et al. 2014).

Critics question the rather unspecific content of such programs and call for programs to be more clearly and differently tailored to the specific coping problems associated with chronic illness, because research findings suggest that focusing solely on problem-solving skills and the associated range of skills may not be sufficient (Haslbeck and Schaeffer 2007).

To date, there are hardly any specific services for lipedema.

One approach is the self-management program offered by Lymphselbsthilfe e. V. since 2009, which was evaluated in 2018/2019 based on the subjective assessment of the participants. At the end of the workshop, they reported that they were better informed and felt subjectively better able to cope with the disease.

9.3.1 The INSEA self-management program "Live healthy and active"

INSEA stands for "INitiative for Self-Management and Active Living" and was developed to promote self-management for people with chronic diseases. It is evidence-based (based on the subjective assessment and feedback of participants) and licensed.

Part of the concept is to provide joint training for a wide variety of conditions; specific content relating to lipedema is not included.

9.3.2 Self-management programs for lipedema

The self-management program offered by Lymphselbsthilfe e. V. (Lymph Self-Help Association), "Gesund und Aktiv Leben mit Lip- und Lymphödem" (GALLiLy, Healthy and Active Living with Lipedema and Lymphedema), funded by the AOK, is aimed at patients with lipedema and/or lymphedema (Helmbrecht and Kraus 2021). The self-management components are similar to the INSEA programs, and the technical content has been specifically adapted to lipedema. An accompanying evaluation of the GALLiLy courses in 2018-2019 focused, like the INESA programs, on participant satisfaction with the training program. The feedback from most course participants was positive in this regard. 85% of participants (n = 122, of whom 21 had a diagnosis of lipedema and 55 had a diagnosis of "lipedema and lymphedema") felt subjectively better equipped for self-management after the course (Helmbrecht and Kraus 2021). Data on medium- to long-term effectiveness is currently being collected and is being evaluated (as of December 2022).

To date, there are only a few services specifically aimed at women diagnosed with lipedema. Often, the services address both women with lymphedema and women with lipedema.

Self-management training for lipedema should include the following content:

- Stress management
- Physical activity, ideally sports, if possible with compression, to reduce pain symptoms
- Improving fitness by gradually increasing physical activity
- Avoiding obesity, stabilizing weight, and avoiding diets due to diet failure. If necessary, additional professional help should be sought.
- Compression as a further basis for therapy: including recognizing when compression is appropriate, the importance of wearing compression daily: information about the appropriate compression class, multi-part supplies if necessary, practice putting on the compression garments with the help of a specialist at a medical supply store, dressing aids
- Information about adjustments to compression garments that do not fit properly. Pain should not be tolerated.
- Options for involving your partner or calling in a care service
- Self-bandaging if compression stockings are insufficient or not (yet) available
- Exercise while wearing compression garments: aqua fitness is particularly effective, as it activates the muscles and joints
- Skin care, as compression puts a lot of strain on the skin: e.g., healthy, clean, moisturized skin; rich creams depending on skin type
- Plan active breaks

- Self-treatment, including mobilization exercises, shoulder circles, breathing therapy/breathing exercises
- The patient remains responsible for their own care: support from others should be recommended.
- Identify sources of support, e.g., when prescribing new compression stockings, for weight management, ask about support in the patient's environment, such as a supportive partner, family, or network, self-help group. Referral to psychotherapy if necessary.

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10 Nutrition and weight management

Gabriele Faerber

Recommendation 10.1

	Level of recommendation	Agreement
Information about the adverse effects of obesity on lipedema and the importance of a healthy diet and an active lifestyle **should** be provided at an early stage.	↑↑	Strong consensus (100%)

Recommendation 10.2

	Recommendation	Agreement
Patients **should** be informed that if they are overweight or obese, leg volume can also be reduced through weight loss with a suitable diet.	↑↑	Strong consensus (100%)

Recommendation

	Recommendation	Agreement
Nutrition and weight management **should** help to maintain or restore mobility and functionality and prevent the disease from progressing. Depending on the individual situation of the patient, the goals **should** therefore **be** to achieve or maintain a healthy body composition, while reducing pain and discomfort.	↑↑ ↑↑	Strong consensus (100%)

Recommendation 10.4

	Recommendation	Agreement
The treatment of overweight and obesity **should be included** in the overall treatment plan for lipedema, as both can lead to progression of limb volume and worsening of the clinical picture.	↑↑	Strong consensus (100%)

Recommendation 10.5

	Recommendation	Agreement
The basis for weight reduction in cases of coincident obesity **should** always be a combination of dietary, These may include exercise and, if necessary, behavioral therapy measures and should encompass both the weight reduction phase and long-term stabilization.	↑↑	Strong consensus (100%)

A large number of lipoedema patients are overweight or obese. Even though lipoedema is thought to be genetically determined, meaning that the disease generally occurs independently of body weight, lifestyle and diet play a role in the symptoms (see Chapter 2). The initial manifestation or worsening of symptoms usually occurs during a phase of hormonal change (Szél et al. 2014), which is often accompanied by weight gain. While weight gain always leads to an increase in limb volume (Forner-Cordero et al. 2021, Frambach et al. 2016), the pain symptoms do not correlate with the severity of the disproportion or the increase in subcutaneous adipose tissue. They can be influenced positively or negatively by a number of other factors, including hormonal changes, diet, psychological factors, and exercise.

However, coincident obesity can lead to reduced mobility and further comorbidities that worsen the overall picture and result in a vicious circle. These include orthopedic complications as well as obesity-associated lymphedema and cardiovascular diseases.

The reduction of excess weight or the treatment of existing obesity while maintaining or achieving a healthy body composition is therefore of great importance in the overall concept of lipedema therapy. Weight management is mandatory, especially in cases of severe obesity and obesity-related diseases.

Depending on the weight situation and the patient's wishes, a conservative or surgical approach may be recommended, whereby the principles of conservative treatment must continue to be followed even after surgical therapy.

Weight reduction should always be based on a combination of dietary, exercise, and, if necessary, behavioral therapy measures and should include both the weight reduction phase and long-term stabilization (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).

An adequate supply of protein should ensure that weight loss does not occur at the expense of muscle mass, but rather at the expense of fat mass. This allows a healthy body composition to be achieved and maintained. This is characterized by an age- and gender-appropriate balance between fat mass and fat-free mass (FFM), in particular body cell mass (BCM). At the same time, the reduction in energy consumption or basal metabolic rate, which is unfavorable for sustainable weight loss, is prevented, and sarcopenic obesity is identified and treated. (Claussen et al. 2022; Ebbeling et al. 2012; Faerber 2014; Larsen et al. 2010).

Since a high proportion of patients have a history of various eating disorders (Erbacher and Bertsch 2020; Stutz 2013), any suspicion of this should be clarified and nutritional therapy should then be provided with psychological support.

Recommendation 10.6

	Recommendation	Agreement
Patients **should** be advised to avoid short-term diets and instead	↑↑	Strong consensus

Permanently change eating habits to a personalized, healthy diet.		(100%)

The fear of many lipedema patients that they will be doomed to constant weight gain due to their condition leads, on the one hand, to numerous frustrating attempts at dieting and a high incidence of eating disorders (Erbacher and Bertsch 2020; Stutz 2013) and, on the other hand, to fatalism with regard to body shape, weight, and obesity. Early education about the clinical picture and the importance of a healthy lifestyle at the time of diagnosis is therefore crucial. With individually tailored nutrition and exercise programs, stable disease progression without significant volume and weight gain can be achieved (Forner-Cordero et al. 2021). The focus should not be on achieving an ideal body weight, but on reducing symptoms, physical well-being, and fitness.

Recommendation 10.7

	Recommendation	Agreement
Patients **should** be informed that Dietary habits have a positive or negative effect on blood sugar and insulin levels and thus on lipogenesis and inflammatory processes.	↑↑	Consensus (94.7%)

10.1 General measures for reducing of additional obesity and inflammation

High insulin levels promote lipogenesis, increase sodium and water retention, and have a pro-inflammatory effect (Blüher et al. 2005; Feinman et al. 2015; Shoelson et al. 2007). Therefore, a diet that avoids blood sugar and insulin spikes and allows for sufficient breaks between meals is recommended for both reducing excess weight and combating inflammatory processes (Amato 2020).

Neuhouser et al. (2012) investigated inflammatory and obesity-associated biomarkers in a randomized crossover study (n = 40 with BMI from 18 to 24.5 kg/m^2 and n = 40 with BMI from 28 to 40 kg/m^2) examined inflammatory and obesity-associated biomarkers under isocaloric diets with high and low glycemic load. Among subjects with high fat mass, the low-glycemic diet significantly reduced hs-CRP by 27%, while adiponectin increased.

Ruth et al. (2013) randomized obese patients to a hypocaloric high-fat low-carb diet (HFLC, n = 26) or a low-fat high-carb diet (LFHC, n = 29) for 12 weeks. While weight loss, lean and fat mass, blood pressure, HBA1C, fasting insulin and glucose did not differ between the groups, the decrease in triglycerides and hsCRP, as well as the increase in HDL and adiponectin, were significantly greater in the HFLC group.

10.2 Special diets for lipedema

Recommendation 10.8

	Level of recommendation	Agreement
A Mediterranean diet (hypocaloric if necessary) **can** be recommended due to its anti-inflammatory properties.	↔	Strong consensus (100%)

There are only a few case reports and small, non-randomized prospective and retrospective observational studies on special diets for lipedema, most of which do not include control groups.

Based on the hypothesis that chronic silent inflammation plays a pathophysiological role not only in obesity but also in lipedema, and that pro- and anti-inflammatory factors can influence symptoms, various authors recommend focusing on combating inflammation in the diet as well, by making patients aware 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 of anti-inflammatory micronutrients such as vitamin D and omega-3 fatty acids EPA and DHA, adjusted to individual levels (Amato and Benitti 2021; Calder 2017; Cannataro and Cione 2020; Carracedo et al. 2019).

A case report describes five female lipoedema patients in stages I-IV who were treated conservatively (Amato and Benitti 2021). In addition to various physiotherapeutic measures, all patients received an anti-inflammatory diet, supplemented with antioxidants, which was not described in detail. One patient subsequently followed a ketogenic diet. The improvement in symptoms was assessed using the Lipedema Symptom Assessment Questionnaire (QuASiL) and ranged between just under 35% and 78%, in some cases after just one month, with volume reduction ranging from 1,230 mL to over 10,000 mL, depending on the stage. In their conclusions, the authors postulate that non-surgical treatment of lipedema in the form of an interdisciplinary, patient-centered approach involving various specialist and professional groups can be successful.

Di Renzo et al. (2021) investigated the effects of a modified, hypocaloric Mediterranean diet (mMeD, calorie deficit 20%) over four weeks in a total of 29 patients, (n = 14 in the lipedema group; n = 15 in the control group) on body weight and body composition, as well as changes in general health, pain experience, fatigue, and functionality in daily life in the lipedema group. The groups did not differ in terms of BMI, but did differ in terms of waist-hip ratio. Both groups significantly reduced body weight and BMI. The lipedema group showed a significant decrease in fat mass in the upper ($p= 0.048$) and lower extremities ($p= 0.007$). There was no difference between the groups in terms of lean body mass. In the lipedema group, the ability to perform daily physical activities improved due to the decrease in fat mass in the extremities, resulting in a significant improvement in quality of life from 8.3 ±1.8 to 6.9 ±1.4 ($p < 0.05$) in the "European Quality of Life" tool (EQ-5D). This is the first time that the effectiveness of a mMeD has been demonstrated both in terms of reducing lipedema fat tissue and improving physical abilities.

Recommendation 10.9

	Recommendation	Agreement
A ketogenic diet (hypocaloric if necessary) **can be recommended** be recommended because it has been shown to have weight-reducing, anti-inflammatory, and symptom-reducing effects have been described.	↔	Consensus (94.7%)

For information on the different forms of ketogenic diets, please refer to the S1 guideline Ketogenic Diets of the Society for Neuropediatrics (AWMF, No. 022-021, 2021).

In a detailed review, the authors put forward several hypotheses on the effect of a ketogenic diet on lipedema (Keith et al. 2021). The effects they observed include weight loss and reduction of fatty tissue in areas typical of lipedema, pain reduction independent of weight loss, and improvement in quality of life. They also postulate, among other things, an anti-inflammatory effect of beta-hydroxybutyrate (BHB) and positive effects in terms of the interactions between metabolic and hormonal changes, namely between estradiol and insulin, and conclude that the ketogenic diet should be further researched as a promising form of therapy for lipedema.

In another review, the authors hypothesized that a ketogenic diet is more effective than other diets for lipedema because it more effectively combats or prevents inflammation due to the complete absence of pro-inflammatory blood sugar spikes (Cannataro and Cione 2020).

In a case report, the same authors report on an obese lipedema patient who, during a 22-month nutritional therapy with a hypocaloric KD (-250 kcal), reduced her weight by 41 kilograms as well as all circumferential measurements and her pain (VAS from 9.2 to 3, -67.39%) (Cannataro et al. 2021). In terms of quality of life, all questionnaires used showed significant improvements (RAND36 in all domains, WOMAC -53.33%, SQS -48.65%). HOMA-IR, a measure of insulin resistance, decreased from 7.16 to 2.44. The authors see this progression as a first step toward a ketogenic diet protocol specifically for lipedema.

A Polish working group compared the effects of a low-carbohydrate, high-fat diet (LCHF) with those of a moderate-carbohydrate, moderate-fat diet (MCMF) with a low glycemic index on the body composition of 91 lipedema patients (Jeziorek et al. 2022). Forty-four percent of the patients had stage I, 42% had stage II, and 13% had stage III. The patients were divided into two groups and assigned to one of the two diets for 16 weeks and received detailed nutrition plans. Both diets had an energy deficit of 15 to 25% depending on the degree of obesity, as well as a high proportion of anti-inflammatory micronutrients and monounsaturated and polyunsaturated fatty acids.

At the beginning and end of the observation period, height, body weight, body fat percentage, fat mass, lean mass, visceral fat, and limb circumferences were measured. The two groups did not differ in terms of anthropometric measurements at the start of the study. In both groups, all anthropometric parameters decreased after 16 weeks, with the exception of the distal lower leg circumference on the right in the MCMF group, but the LCHF-

Nutrition in relation to 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 of the MFMC diet.

The disproportion between the upper and lower body decreased, although less significantly under MCMF. Pain and edema reduction, as well as improved mobility and subjective quality of life, were also observed in the LCHF group, in contrast to the MCMF group. The data on this were not published.

Another prospective study compared the effects of a personalized, ketogenic diet reduced by 15-25
% calorie reduction diet over seven months on metabolically relevant laboratory parameters in overweight or obese patients (n=24) versus patients with lipedema (n=24) (Jeziorek et al. 2023). 54% of lipedema patients were in stage II. While waist circumference was significantly higher in the overweight group than in the lipedema group at the start of the study, body weight, hip and leg circumferences did not differ, and the waist-hip ratio was lower in the lipedema group. There were also no differences between the groups in terms of laboratory values, with the exception of significantly higher LDL-C levels in the overweight group.

Both groups reduced their body weight. While triglycerides decreased significantly and HDL cholesterol increased in both groups, the effect on LDL-C was inconsistent among individuals. Liver function, glucose tolerance, and fasting insulin improved in both groups, although less pronounced in the lipedema group. Kidney and thyroid function remained unchanged in both groups. The authors conclude from these results that a low-carbohydrate, high-fat diet may be a valuable nutritional strategy for both lipedema and overweight patients, as it has a positive effect on body weight, glucose profile, liver values, and HDL without impairing thyroid and kidney function, and also has anti-inflammatory effects.

Faerber has reported several times on the effectiveness of such a ketogenic diet on leg volume, weight, and pain reduction (Faerber 2017a; Faerber 2017b; Faerber 2018). In a retrospective study of 92 lipedema patients, symptoms decreased from 6.5 ± 3 to 2 ± 2 (-69.23%, p<0.01) on an NRS, regardless of weight loss and even in patients of normal weight. All measured circumferences were significantly reduced (between 9.64% on the lower leg and 12.83% on the proximal thigh; p < 0.001; effect size -0.93 to -1.27). Both the subjective reduction in the feeling of heaviness and tension and the changes in tissue observed by the treating physical therapists began after just a few days and long before any relevant weight loss.

Several studies in rodents have shown positive effects of a ketogenic diet on pain (Cooper et al. 2018; Masino and Ruskin 2013; Ruskin et al. 2021).

Sørlie et al. conducted a pilot study on the effect of a normocaloric KD on pain and quality of life in overweight lipedema patients (BMI 30–45 kg/m^2)(Sørlie et al. 2022). Once again, the limitations of the study lie in the small number of cases (n = 9) and the lack of a control group, so that, in the authors' opinion, the results should be interpreted with caution.

as participation in the study alone could have an effect. The patients were given a ketogenic, normocaloric diet for 7 weeks, followed by a six-week diet in accordance with the Nordic Nutrition Recommendations (NNR). Pain (VAS) and QoL (Norwegian Questionnaire for Lymphedema of the Limbs), weight, and body composition were measured at the beginning, after 7 weeks, and after 13 weeks. Despite the lack of a calorie deficit, the patients lost 4.6 ± 0.7 kg by week 7 ($p < 0.001$), partly due to a decrease in total body water (TBW). Pain intensity (VAS) improved by 2.3 ± 0.4 cm ($p = 0.020$). The reduction in pain did not correlate with weight loss in week seven, which was maintained until week 13, while pain levels rose again to baseline levels in week 13, confirming the authors' finding that the reduction in pain was caused by the KD rather than by weight loss. It remains unclear whether this is due to the ketones themselves, especially beta-hydroxybutyrate, or the altered composition of macro- and micronutrients. A significant improvement in overall QoL was found between baseline and week 7 (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 pain perception and improved QoL in lipedema patients and call for larger randomized studies to confirm these results.

In a prospective case-control study, 56 lipedema patients and 57 overweight or obese women were given a low-carb, high-fat diet with anti-inflammatory properties for 7 months (Jeziorek et al 2023). The study examined not only the effects on body composition and leg volume, but also pain reduction using a visual analog scale. While both groups achieved comparable reductions in weight and circumference, the participants in the lipedema group also showed significantly reduced
pain scores (VAS 4.6± 2.6 vs. 3.0± 2.3).

Verde et al (2023) conclude in a recent review of the effectiveness of a very low-calorie ketogenic diet (VLCKD) in lipedema that VLCKD is an effective treatment option for lipedema, particularly when accompanied by obesity, due to its anti-inflammatory properties, and that combining VLCKD with a Mediterranean diet could further enhance the positive effects.

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11 The importance of bariatric therapy in the treatment of patients with lipedema

Jodok Fink, Till Hasenberg

Recommendation 11.1

	Level of recommendation	Agreement
The indication for bariatric surgery in patients with lipedema **should be determined** in accordance with the S3 guideline "Surgical Treatment of Obesity and Metabolic Diseases." The waist-height ratio **should be taken into account** when determining the indication , as BMI alone is not conclusive in cases of pronounced disproportion With the aim of weight reduction and reduction of leg volume, bariatric surgery **should be considered** in patients with lipedema and a BMI of≥ 40 kg/m2. ≥In patients with lipedema and a BMI between 35 kg/m2 and <40 kg/m2 and at least one other obesity-related disease, bariatric surgery **may be considered.** Procedure aimed at weight reduction and reduction leg volume.	↑↑ ↑↑ ↑ ↔	Consensus (94.7%)

The data available on bariatric therapy for lipedema is extremely limited.

In preparing these recommendations, the current S3 guideline: Surgical Treatment of Obesity and Metabolic Diseases (DGAV) (German Society for General and Visceral Surgery (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 guideline: "Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update" (AACE) (Mechanick et al. 2020) have been included.

The largest available meta-analysis on the effectiveness of bariatric surgery in patients with obesity compared to conservative therapy for weight loss includes 25 randomized controlled trials. This shows a highly significant and sustained advantage for bariatric surgery in terms of weight loss (Cheng et al. 2016). In 16/25 studies, the primary endpoint was not weight but type 2 diabetes. Another meta-analysis of a total of 11 randomized controlled trials involving 796 patients clearly showed that patients had significantly greater weight loss after bariatric surgery than after conservative therapy (Gloy et al. 2013). Weight loss after bariatric surgery was 27 kg greater. In addition, there was a higher remission rate for type 2 diabetes mellitus and a greater improvement in quality of life. The main

side effects of bariatric surgery in this meta-analysis were iron deficiency anemia (15%) and reoperations (8%).

Long-term data from randomized studies are not available. Nevertheless, long-term data from a large prospective cohort study show a persistent, significant advantage of bariatric surgery over conservative therapy in terms of weight loss, incidence of type 2 diabetes, and improved oncological outcomes (Sjöström 2013). Conversely, an analysis of the conservative cohort from the same study over a period of 10 years documented persistent, unsuccessful attempts by patients to reduce their weight: 54.6% showed weight gain, while only 12.5% showed a decrease of more than 10% of their body weight (Zenténius et al. 2018).

There are no randomized controlled trials on bariatric surgery in patients with lipedema. However, a retrospective cohort study in this patient group clearly shows that patients with lipedema can achieve similar weight loss after bariatric surgery compared to overweight controls (Fink et al. 2021).

Further evidence on bariatric surgery with the aim of weight loss and improvement of metabolic diseases is summarized and evaluated in the S3 guideline: Surgical Treatment of Obesity and Metabolic Diseases as well as the EAES and AACE guidelines (German Society for General and Visceral Surgery (DGAV) 2018; Di Lorenzo et al. 2020; Mechanick et al. 2020).

According to all three guidelines cited above, bariatric surgery is recommended regardless of comorbidities for patients with a BMI of 40 kg/m² or higher(German Society for General and Visceral Surgery (DGAV) 2018; Di Lorenzo et al. 2020; Mechanick et al. 2020). For patients with a BMI of≥ 35 kg/m(2) to< 40 kg/m(2), the DGAV, EAES, and AACE guidelines indicate bariatric surgery in the presence of obesity-related comorbidities (German Society for General and Visceral Surgery (DGAV) 2018; Di Lorenzo et al. 2020; Mechanick et al. 2020). Lipedema is a possible coincidental disease but, according to the S3 guideline on bariatric therapy, it is not an obesity-related comorbidity in the sense of an indication for bariatric surgery. When evaluating a bariatric procedure, the disproportionate distribution in patients with lipedema with a comparatively smaller waist-to-height ratio (WHtR) and thus potentially reduced metabolic risk should be taken into account (Bertsch et al.
2020; Brenner and Cornely 2022; Brenner et al. 2023).

There is little data available on the specific effectiveness of bariatric surgery on lipedema. There are two case reports with four patients each and another report that primarily considers medico-legal aspects in the diagnosis of lipedema (Bast et al. 2016; Pouwels et al. 2018; Pouwels et al. 2019). The main data is based on a retrospective cohort study of 31 patients with lipedema (Fink et al. 2021) and a retrospective case series of 13 patients (Cornely et al. 2022). The case reports point to certain limitations of bariatric surgery, with leg volume remaining unchanged in some cases despite weight loss (Bast et al. 2016; Pouwels et al. 2018; Pouwels et al. 2019). However, the retrospective cohort study clearly shows that leg volume decreased significantly. The reduction in leg volume was comparable to that of control patients without lipedema (Fink et al. 2021). Accordingly, a practice guideline from the UK also mentions bariatric surgery as a possible option for weight reduction in patients with lipedema (Hardy and Williams 2017).

Data on lipedema symptoms (pain) after bariatric surgery can be found in a
case series involving 13 patients who were diagnosed with lipedema after bariatric surgery and were then asked retrospectively about their symptoms prior to bariatric surgery. This shows that pain persisted despite good weight loss (Cornely et al. 2022).

No data on the type of bariatric surgery is available, so no recommendation can be made at the time of writing the guideline.

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12 Surgical treatment of lipedema

Manuel Cornely, Stefan Rapprich

12.1 Liposuction

Recommendation 12.1

	Degree of recommendation	Agreement
Liposuction **should** be used as the surgical method of choice for the permanent reduction of subcutaneous fatty tissue affected by lipoedema on the legs and arms.	↑↑	Consensus (84.2%)

12.1.1 Indication

Liposuction for painless lipohypertrophy of the extremities is not covered by this guideline.

Recommendation

	Level of recommendation	Agreement
The following aspects regarding the indication for surgical treatment by liposuction in cases of lipedema of the legs and/or arms should be taken into account: arms **should** be considered: • Documented refractory pain – no improvement despite conservative therapy • Complications such as restricted mobility, dermatological or orthopedic sequelae • Critical indication with a waist-height ratio (WHtR) above 0.55 and a BMI above 40 kg/m² • Prior treatment of coincident obesity • Preoperative decongestion in cases of coincidental edema of other origins • Strict indication for patients under 18 years of age	↑↑	Consensus (94.4%)

Recommendation 12.3

	Degree of recommendation	Agreement
Indications for liposuction **should** no longer be based on the conventional staging system, as there is no correlation between the severity of symptoms and stage classification.	↑↑	Strong consensus (100%)

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

Decongestive therapy should be performed prior to surgery if clinical evidence of edema is present. If there is no evidence of edema, preoperative decongestive therapy is not necessary. It has no influence on the outcome of liposuction treatment.

Surgeons experienced in liposuction recommend critical indication in cases of a BMI > 40 kg/m² and a WHtR above 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).

If obesity and lipedema occur together, the obesity should be treated (Kruppa et al. 2020; Rubin et al. 2012; Wollina and Heinig 2019). (German Obesity Society (DAG) 2014). Liposuction of the extremities is not a method for weight reduction (Bertsch et al. 2020; Sandhofer et al. 2020; Sattler et al. 1997).

Patients with lipedema may suffer from restricted movement, which can lead to further orthopedic complications (Stutz 2011). Liposuction can correct axial misalignment by reducing volume, thereby alleviating restricted movement (Wright et al. 2023).

In rare cases of severe lipedema, large, sagging pockets of tissue may remain after successful liposuction. In such cases, subsequent plastic surgery to tighten the skin using a technique that preserves the lymph vessels, such as the AVELAR technique (Avelar 1985; Ghods 2019), may be recommended.

12.1.2 Technique and procedure

Recommendation 12.4

	Level of recommendation	Agreement
Liposuction **should be performed** using a tissue- and lymph vessel-sparing technique The following aspects should be taken into account: • Use of vibration-assisted (PAL) or water-jet-assisted (WAL) systems • Procedure performed under local or general anesthesia • 1-4 sessions on both legs, 1-2 sessions on both arms • Adherence to an exposure time of at least 60 to 120 minutes after infiltration of the TLA to promote gentle aspiration. • Limitation of the tumescent solution used (when using the Klein solution with a maximum lidocaine dose of 45 mg/kg body weight) to 10 liters. • Maximum aspiration volume of 10% of body weight	↑↑	Consensus (94.4%)

Liposuction should be performed under local anesthesia using tumescent local anesthesia (TLA), which prepares the fatty tissue, i.e., using the "wet technique" with blunt microprobes, in order to minimize damage to the lymphatic system (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). Supportive techniques such as vibration or water jets can be used (Stutz and Krahl 2009; Taufig 2003; Taufig 2004). The procedure can be performed on an outpatient or inpatient basis (Working Group on Hospital and Practice Hygiene of the AWMF 2018; Cornely 2000; Cornely 2014; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012). When performing the procedure in TLA, additional analgesic sedation or anesthesia may facilitate the procedure for the patient and surgeon.

Anatomical and clinical studies, functional lymphoscintigraphy, and immunohistochemical examinations of the aspirated adipose tissue confirm that no relevant damage to the lymphatic vessels occurs (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 procedures under general anesthesia with "dry liposuction," such studies are not available.

Liposuction can also be performed 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 used, gentle aspiration of the yellow and therefore blood-poor aspirate is evident (Cornely 2023; Cornely et al. 2022; Ghods and Kruppa 2018; Korsake and Rapprich 2020; Kruppa et al. 2022; Sandhofer et al. 2020).

Properly performed liposuction corresponds to subcutaneous suprafascial subtotal fat tissue aspiration exhairesis. However, it must not lead to skeletonization of the skin, as such radical measures are not necessary to achieve the goal of pain relief. A more radical approach is associated with a high risk of complications (Cornely 2016; Korsake and Rapprich 2020; Sandhofer et al. 2020; Sattler and Eichner 2013).

12.1.3 Follow-up treatment and results

Recommendation 12.5

	Degree of recommendation	Agreement
Immediately after liposuction**,** complex physical decongestive therapy should be performed. The intensity and duration should be based on the postoperative findings. CPT should begin with phase I.	↑	Strong consensus (100%)

Recommendation 12.6

	Degree of recommendation	Agreement
After liposuction, patients **should** continue to receive conservative treatment depending on their symptoms. Particular attention **should** be paid to mobility, weight stability, and stress regulation.	↑↑ ↑↑	Consensus (94.4%)

Lipedema cannot be cured by liposuction. Liposuction **can** permanently relieve pain and improve quality of life.	↔	

The procedure leads to marked improvements in spontaneous pain, pressure pain, and hematoma tendency with significant pre- and postoperative differences (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 MeierVollrath 2007). A reduction in conservative therapy, and in some cases even freedom from therapy, is achieved (Cornely 2004; Cornely 2014; Rapprich et al. 2015; Rapprich et al. 2011; Schmeller et al. 2012). The majority of improvements in findings remain consistent over 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).

The success rate of the techniques described above is between 92 and 97 percent in two surgical centers in Germany. The follow-up periods for the more than 325 patients were up to 15 years, and no recurrences occurred (Cornely 2004; Cornely 2007; Cornely 2014; Rapprich et al. 2015; Rapprich et al. 2011).

Even though the morphological staging system used to date does not reflect the severity of the disease (Brenner 2023, Cornely 2023, Brenner et al. 2023), surgical outcomes are better in earlier stages than in stage 3 (Kruppa et al. 2022).

Furthermore, the reduction of fatty tissue deposits on the inner thighs and knees reduces or eliminates mechanical and occlusive skin damage. Correcting the leg misalignment caused by fat deposits in the extremities improves mobility and gait (Stutz 2011) and reduces the risk of further orthopedic complications resulting from the pathological gait associated with lipedema (e.g., gonarthrosis and coxarthrosis).

The reduction in symptoms, increased mobility, less time required for conservative therapy, and renewed self-confidence significantly improve the quality of life of those affected (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 liposuction for medical or cosmetic reasons have been reported, but are rare.

- A multicenter American study on liposuction in TLA in 15,336 procedures reported a complication rate of 1.12% in 1995 (Hanke et al. 1995).
- In a series of 3,240 procedures, there were no deaths and no complications requiring hospitalization. In nine cases (0.27%), complications requiring further treatment occurred (Habbema 2009).

- Kruppa et al. reported a complication rate of approximately 9.5% for all liposuctions in 2020. Bleeding complications accounted for 1%, wound infections for 4.5%, and the development of erysipelas for a further 4% (Kruppa et al. 2020).
- In another retrospective study, Kruppa et al. reported a complication rate of approximately 2.3% for all liposuction procedures in 2022. Bleeding complications accounted for 0.3%, wound infections for 1.3% and the development of seroma for a further 0.7% (Kruppa et al. 2022).
- Kanapathy et al. report on 3,583 patients in their meta-analysis. The overall incidence of major surgical complications was 3.35%. The overall incidence of minor surgical complications was 11.62%, with seroma being the most common minor complication (5.51%) (Kanapathy et al. 2021).

Complications after liposuction due to lymphatic vessel injury are rarely recognized and therefore reported less frequently or not at all in the literature (Sandhofer et al. 2020). An incidence of 1.7% is reported for swelling that persists for more than 6 weeks after liposuction (Dixit and Wagh 2013).

This swelling could represent delayed healing, but could also include patients with lymphatic vessel injury. Most of the skin complications reported to date following liposuction begin with hyperemia and/or pallor of the skin, followed by skin necrosis and ulceration in the early postoperative period, or are associated with infection and/or poor skin healing. Wright reports on three women with lipedema who developed lymphedema after liposuction. The typical skin changes did not appear until 6 months to a year after the operation and correspond to the definition of chronic skin changes in lymphedema (Wright and Herbst 2022).

Surgery to reduce lipedema is therefore not without risk 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 due to the surgical technique:

- In a study examining the lower extremities of fresh cadavers, dry suction lipectomy with blunt cannulas using a longitudinal technique caused either no or only moderate injury to the lymphatic collectors (Frick et al. 1999; Hoffmann et al. 2004).
- In contrast, the use of a transverse technique regularly caused moderate to severe injury to the lymphatic vessels. When tumescent anesthesia was used prior to liposuction, the longitudinal technique resulted in either no or moderate injury, and the transverse technique rarely resulted in severe injury.
- Liposuction performed under general anesthesia and/or with relatively low subcutaneous infiltration carries an increased risk of damage to the lymphatic system (Wright and Herbst 2022).

Complications following lipedema reduction surgery are also rarely reported in the US. Complications reported by participants in the study included

anemia, deep vein thrombosis, pulmonary embolism, lymphedema, pneumonia, cellulitis (erysipelas), skin irritation, tissue or skin folds, asymmetry, and sagging skin. The largest percentage of participants had no complications. It is unclear whether the patients who developed lymphoedema did so as a result of the procedure or over time due to an underlying lymphatic dysfunction. Close and long-term monitoring of patients with lipedema after surgery is necessary (Herbst et al. 2021a, Herbst et al. 2021b).

A postoperative examination of 1,400 lipedema patients in Germany who underwent surgery under Superwet-TLA and accompanying analgesia or general anesthesia revealed 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 liposuction procedures performed to treat lipedema (Schmeller et al. 2012). Rapprich reports only 1 case of deep vein thrombosis during 15 years of surgical treatment of lipedema (Rapprich et al. 2012). In general, liposuction using the tumescent technique carries a low surgical risk and has proven to be a safe and appropriate procedure.

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13 Appendix 1: Screening

13.1 Screening for relevant and common psychological stressors, in accordance with the recommendations of other guidelines

The use of clinical questionnaires can be helpful as a screening tool when the severity of patients' problems needs to be assessed or when the practitioner wants to confirm their own impression more objectively (Schulte 2011).

License-free questionnaires that are freely accessible as open access and easy to evaluate are helpful and pragmatic in everyday practice. They are intended to make it easier for physicians without psychotherapeutic training in particular to assess the treatment needs of patients with lipedema.

S3 guidelines for diagnosis and treatment already exist for mental disorders that are significantly more common in women with lipedema than in the general population (depression, eating disorders, and post-traumatic stress disorder (Dudek et al. 2018; Erbacher and Bertsch 2020). The following recommendations, which have already proven themselves in the practical diagnosis and treatment of women with lipedema, are therefore consistent with the recommendations of the S3 guidelines on the diagnosis and treatment of unipolar depression (DGPPN et al. 2015), for the diagnosis and treatment of eating disorders (DGPM et al. 2018), and for the diagnosis and treatment of post-traumatic stress disorder (Schäfer et al. 2019) (as of January 2021).

In general, it is extremely important in any psychodiagnostic screening to depathologize the patient's thoughts, feelings, and behaviors. For example,
uncontrolled eating/binge eating can be described as a "coping mechanism," "psychological rescue attempt," or "stress management" in cases of psychological distress. This normalized description of the function of the symptom (e.g., binge eating) makes it easier for the patient to open up. Difficult topics that are often associated with shame or guilt—such as loss of control over eating—can then be addressed more effectively (e.g., binge eating). (DGPM et al. 2018).

Patients suffering from a mental disorder, such as depression, often do not report it themselves. Depression in particular should therefore be proactively inquired about (DGPPN et al. 2015). If a mental disorder is suspected, practitioners who are not trained in psychotherapy can then refer the patient to appropriate specialists (psychological or medical psychotherapists).

As a rule, the psychological abnormalities or disorders exhibited by women with lipedema are highly modifiable. Experience has shown that this information provides significant psychological relief for patients.

The screening diagnostics mentioned below represent a selection of suitable procedures that could be used to supplement diagnostics and monitor progress. Liability lies with the user. Screening does not replace psychodiagnostics by a specialist in psychotherapy or psychiatry or a psychological psychotherapist.

13.1.1 Screening for lipedema-associated pain:

- **Visual analog scale** (VAS) (Funke 2010) for assessing lipedema-associated pain, as recommended by the Dutch Lipedema Guideline (Dutch Society for

Dermatology and Venereology (NVDV) 2014). This is a 10 cm long line/scale on which the patient is asked to rate their pain intensity between 0 "no pain" and 10 "the worst pain imaginable, comparable to amputation pain":

- Ask about the maximum pain intensity within a certain period of time (e.g., the last week).
- Ask about the minimum pain intensity within this period (e.g., the last week)

In addition to assessing pain intensity, assess **Subjective Units of Disturbance (SUD)** using the visual analog scale:

- How much do you suffer from this pain (0-10 scale)?

Even if the pain is mild, it can have a quality that some women with lipedema find very distressing. On the other hand, there are also a few women with lipedema who describe the pain they experience as severe but the suffering they endure as mild or moderate.

13.1.2 Screening for depression*:*

A two-question test, a very time-efficient pre-screening that identifies unipolar depression with a sensitivity of 96% and a specificity of 57% (Whooley et al. 1997) according to the S3/NVL Unipolar Depression (DGPPN et al. 2015):

1. Have you often felt down, sad, depressed, or hopeless in the last month?
2. Have you had significantly less interest or pleasure in things you usually enjoy doing in the last month?

Hospital Anxiety and Depression Scale (HADS) (Bjelland et al. 2002; Zigmond and Snaith 1983), a frequently used method, but with the risk of high scores even without clinically manifest depression, i.e., false positive results.

The following cut-off values apply:≤ 7: clinically unremarkable, 8-10: suspicious, >10: clinically relevant 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 uses 4 subscales (22 items). The subscales "Restrained Eating" and "Eating Concern" describe abnormalities in eating behavior such as restrictions in food intake, following diet rules, or feelings of guilt when eating. The scales on "Weight Concern" and "Shape Concern" explore whether there is a negative body image and whether shape and weight are of increased importance for self-esteem. In addition, binge eating and compensatory measures are also assessed.

Available at: https://docplayer.org/24385400-Eating-disorder-examination.html

13.1.4 Assessment of quality of life

- **SF-36** for assessing health-related quality of life (Bullinger 2000; Morfeld et al. 2011), a tool that is frequently used in research and for monitoring quality of life and whose suitability for assessing quality of life specifically in women with lipedema has been confirmed in comparison to individuals with lymphedema (Angst et al. 2020). It comprises eight domains: vitality, physical functioning, physical pain, general health perception, physical role functioning, emotional role functioning, social functioning, and psychological well-being. The SF-36 profiles of different diseases differ significantly, e.g., the profiles of patients with lipedema and patients with fibromyalgia (Angst et al. 2021). The values reported by Angst et al. (2021) for women with lipedema could currently serve as SF-36 reference values until specifically developed reference values for lipedema are available.

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