Thick legs – not always lipedema

Summary
Due to its increased presence in the press and on television, the diagnosis of lipedema is on the way to becoming a trendy diagnosis for those with thick legs. Despite this, one must recognize that lipedema is a very rare disease. It is characterized by disproportional obesity of the extremities, especially in the region of the hip and the legs, hematoma development after minimal trauma, and increased pressure-induced or spontaneous pain. Aids for making the correct diagnosis are (duplex) sonography, the waist-hip index or the waist-height index and lymphoscintigraphy. Important differential diagnoses are constitutional variability of the legs, lipohypertrophy in obesity, edema in immobility, edema in chronic venous insufficiency and rheumatic diseases.

The symptom-based therapy of lipedema consists of conservative (compression, manual lymphatic drainage, exercise) and surgical treatments (liposuction). Until now there is no curative therapy. Obesity is an important risk factor for the severity and prognosis of lipedema. Further studies for a better understanding of the pathogenesis of lipedema and in the end possible curative treatments are urgently needed.

Introduction
As recently as a few years ago, the term “lipedema” was virtually unknown in the medical field [1]. Since the lay press and media such as television and the internet have discovered this diagnosis and have presented some in part very sensational reports, it has almost become a trendy diagnosis. Currently not a day goes by in offices or outpatient services with a lymphologic focus without at least one patient with obesity and extensive lipohypertrophy presenting, who has been diagnosed by a colleague lacking lymphologic experience incorrectly with the diagnosis lipedema, or who would enjoy having the diagnosis lipedema in order to finance manual lymphatic drainage and liposuction by the statutory or private health insurance. Further, there are women with rather thick legs, but without any complaints, who are frightened by the diagnosis lipedema because of the images circulating in the internet on this subject and the apparently fatalistic prognosis associated with lipedema.

Such a misdiagnosis is frustrating for all involved and imprudent in face of the responsibility for the patient and the requirement to provide economic therapy. We discuss the diagnostic approach to lipedema, its most important differential diagnoses and the resulting different consequences.

What is lipedema?
The term “lipedema” is misleading, as it is not edema, i.e. fluid deposition in tissue. Lipedema is usually a genetically determined disturbance of adipose tissue mass and distribution that was reported many years ago [2]. In the presence of a slender trunk and waist – usually after puberty or sometimes only after pregnancy – a disproportionate and symmetric deposition of adipose tissue develops in the gluteal and hip region as well as on the legs (about 97 %) and/or on the arms (about 30 %) [3]. Typically, the feet and hands are spared [4]. It has not been definitively determined if this is a result of hypertrophy or hyperplasia of adipocytes or a combination of both phenomena [1]. Activated adipogenesis in lipedema tissue is suspected leading to hypoxia and consecutive adipocyte necrosis and recruitment of macrophages, as is known in obesity [5].
The tissue is tender to pressure and likely develop hematomas after even the slightest trauma.

As it is not primarily fluid-induced increased volume, the swelling tendency and increased circumference is typically not reversible or reducible over night or upon elevation of the limb. Only an additive orthostatic edema component of the typical increased capillary permeability will regress over night [6, 7].

During the course of the disease spontaneous pain can develop leading to distinctly impaired mobility. Pain alone is, nonetheless, not a sufficient differential diagnostic criterion, as pain cannot be objectified. In view of the different previous information of the patient via various media with the resulting list of all possible symptoms found there, the common lack of complaint of pain in the manual compression test during physical examination makes assessment of actual tenderness or pain difficult.

As a result of disproportionate adipose tissue increase of the legs, in advanced cases gait disturbances and joint deformities (e.g. genu valgum) may develop.

Skin color is unaltered in uncomplicated lipedema. Erythema and hyperpigmentation only occur as a result of complications such as stasis dermatitis or functional chronic venous insufficiency in accompanying obesity. Further, pure lipedema is not a typical sequel of obesity such as arterial hypertension, metabolic disorders or diabetes mellitus [1]. Therefore another type of adipocytes and altered receptors are assumed in lipedematous adipose tissue. At the same time associated obesity is, nonetheless, observed in about 50 % of patients [8].

Women almost exclusively are affected by lipedema after puberty [1]. Data on the actual prevalence are difficult to obtain and vary depending on the clientele studied and the author between 1:72,000 and 1:5 in the female population [3, 9, 10]. Overall, it does constitute a very rare disease. The cause of lipedema is unknown. X-linked or autosomal dominant inheritance with a sex-specific limitation are possibilities [9].

**What diagnostic steps lead to the diagnosis lipedema?**

The diagnostic approach to lipedema includes at a minimum a comprehensive history and complete physical examination with consideration of proportional circumference and/or size parameters as well as sonography. Further imaging diagnostics (CT/MRI) and functional lymphoscintigraphy can be helpful in refining the diagnosis.

Despite numerous studies with histology, lymphoscintigraphy, phlebography, MRI and lymphangiography, no diagnostic procedure has demonstrated specific signs of lipedema [9]. In the end the differential diagnosis depends on the clinical experience of the physician [11].

**History**

There is usually a history of slowly progressive increase in circumference of the legs and/or arms following puberty or early adulthood. The women complain of pressure-induced pain at even slight contact and a tendency to develop apparently spontaneous hematomas [1, 12]. Many women who would like to be diagnosed with lipedema have performed a detailed internet search and are very aware of the appropriate symptoms. Positive responses in the history must therefore be verified through clinical inspection (hematomas) and particularly by palpation (tenderness or pain).

**Inspection and palpation**

The clinical examination reveals especially in advanced stages a distinctly altered skin relief with an orange-peel appearance, puckering and doughy subcutaneous nodules (Figure 1) [12]. Usually – in the absence of associated lymphedema – no pitting develops on pressure, the Stemmer sign is negative, and the dorsa of the hands and feet are not involved. In the vicinity of the joints, usually at the ankles, but also on the knees and hand joints, the key morphologic criterion of
the typical step (Figure 2) is seen. The appearance is that of harem pants with an elastic band.

High-resolution sonography

Sonography reveals broadening of subcutaneous adipose tissue with a significantly denser echogenic structure (“snow flurries”) with echo-rich connective tissue septa in comparison to uninvolved sites [13]. Fluid-filled clefts cannot be detected in pure lipedema but only after development of lipolymphedema [14]. Lymphoscintigraphy reveals completely normal or initially even increased lymphatic drainage.

Marschall and Schwahn-Schreiber proposed a classification of the severity of lipedema on the basis of sonometric criteria [10]: The thickness of the subcutis including the cutis is measured 6–8 cm above the medial malleolus; this is a reliable point of reference even in proximally accentuated lipedema:

- 12–15 mm = mild lipedema or lipohyperplasia
- 15–20 mm = moderate lipedema
- >20 mm = distinct lipedema
- (>30 mm = severe lipedema).

The cutis thickness in healthy individuals can be up to 2.1 mm.

In our experience, obese persons can have similar values without other criteria of lipedema being present, so that the proposed values can lead to the misdiagnosis of lipedema.

Index determination

The BMI can be misleading, as it takes total weight into consideration, but not the disproportionate distribution in the high-weight body regions [9]. Therefore many women are seen with an apparently overweight BMI >25.

Additionally, the waist-hip ratio should be determined. In normal-weight patients this lies <0.8 (in women) or <0.9 (in men). Values >0.85 in women and >1.0 in men denote obesity – even with lipedema [15].

A further option is the determination of the waist-height ratio. For persons under 40 years a value of >0.5 is pathological and thus a diagnostic criterion for obesity. In the age of 40 to 50 years the threshold lies between 0.5 and 0.6, in the 50-year-olds at 0.6. Lipedema patients have quotients below these limits.

Lymphoscintigraphy/ MR lymphangiography

Lymphoscintigraphy is reserved for special questions and plays no role in the routine clinical diagnosis of lipedema. It serves at best to exclude associated disturbance of lymphatic drainage. From comprehensive studies, it is known that in the initial stages of lipedema even an increased lymph transport can exist. Only when the increased lymphatic burden exceeds the available transport capacities for years or decades, does decompensation occur and a lipolymphedema develop [16, 17].

An alternative or supplement can be MR lymphangiography [18]. It, too, is particularly suitable for determining the degree of lymphatic involvement in lipedema or lipolymphedema.

Diagnostic criteria of lipedema

Unfortunately, to date only few hard criteria for diagnosing lipedema exist. The diagnosis often depends on the clinical experience of the physician. Nonetheless, in our experience, a series of exclusion criteria that speak against the presence of typical lipedema exist (Table 1). This exclusion catalog can also be useful for those with less experience in diagnosing lipedema.

Table 1 Exclusion criteria for lipedema. A typical lipedema can be excluded with at least one negative criterion.

- Lack of disproportion between upper and lower body
- Asymmetry of both legs/ arms
- Manifestation in late adulthood
- Waist-hip ratio >0.85 in women/ >1.0 in men
- Waist-height ratio: <40 years: >0.5 pathological; 40 to 50 years: 0.5–0.6 pathological; >50 years: >0.6 pathological
- Lack of step formation in the ankle region
- Lack of pressure-induced pain of tissue
- Lack of tendency to develop hematomas
- Subcutis thickness <12 mm (6–8 cm above the malleolus)
lipedema. In some cases in daily clinical routine mixed features of lipedema and obesity or lipedema and lymphedema are seen. Nevertheless, the majority of putative cases of lipedema that actually reflect another diagnosis can be excluded on the basis of these criteria.

What are the therapeutic options for lipedema?

Not surprisingly, as the cause of lipedema is still unknown, no curative therapy is known [12]. In view of the uncertainty of patients and physicians with respect to the disease, frequently absurd measures such as diuretics and laxatives are prescribed [1]. These are not indicated for lipedema.

The goal of treatment is therefore improvement of the subjective symptoms, prevention of progression of lipedema and prevention of the development of lipolymphedema (Table 2).

The therapeutic measures should be adapted to the severity of clinical findings, the level of suffering and the wishes of the patient and be combined in a sensible therapy plan according to the current guidelines [12]. Comprehensive patient counseling is essential; it often must be repeated. In the event of lack of understanding or insufficient information about the disease, both the treating physician and the affected patient may develop unrealistic expectations, insecurity and dissatisfaction.

Compress therapy – aim: reduction of edema, reduction of mechanical impairment of walking, reduction of pain

Compression therapy can in early stages be performed with round-knitted compression stockings; as the disease progresses and steps form in the joint region, flat-knitted compression material is usually required [19, 20]. Round-knitted compression stockings with low material stiffness can lead to restriction in the joint area with development of secondary stasis (Figure 3). Compression therapy can naturally not bring about a reduction of adipose tissue mass, but can prevent additional edema formation and thus reduce the resulting tension and pain. To a small extent it is also possible through compression therapy to achieve mild remodeling of tissue and improvement of gait. In many cases patients are more mobile with compression than without. Compression therapy can help mobilize patient and thus prevent or ameliorate obesity.

Therapeutic exercise – aim: reduction of associated obesity, reduction of edema

Unfortunately, many patients are uncertain as to how much physical activity they can undertake. Some claim that activity leads to increased muscle mass in the legs, increasing the disproportion between upper and lower body even more [20]. These fears are wrong; physical activity should be encouraged

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Exercise activates the foot and calf muscle pump increasing lymphatic drainage, reducing edema formation in the tissue and reducing the risk of additional obesity.

Suitable types of sport are swimming, speed walking and bicycle riding. Sports with a high risk of injury or strong decelerating movements are often unpleasant and associated with subsequent pain. The cause for this is unclear. Scientifically-based data on sporting activity in lipedema are not available.

**Weight normalization – aim: reduction of associated obesity, reduction of edema**

Weight gain in lipedema is usually not predestined, but fundamentally determined by the general nutritional and exercise behavior. Even though diets and change of nutritional behavior cannot prevent the typical disproportion of lipedema, they can improve the overall appearance and the prognosis. Obesity is a major exacerbating factor of lipedema [21].

**Manual lymphatic drainage (MLD) – aim: reduction of edema, reduction of pain, reduction of tendency to develop hematomas**

As lipedema does not represent a watery or protein-rich edema and in early stages lymphatic drainage is even increased, MLD is not indicated there. It is sensible when, in addition to pure increase in adipose tissue, lipolymphedema also has developed (Figure 4). Indicators of this situation are echo-poor clefts in the tissue in the ankle region detectable by sonography. Particularly in combination with consistent compression therapy, MLD is capable of achieving significant reduction of pain [22] and the tendency to develop hematomas [23].

Of course, MLD even in early stages is pleasant and alleviates pain [20]. There is hardly a therapy prescribed by physicians that promotes well-being more and is therefore demanded vehemently by patients. Nonetheless, in initial phases it has no medically justified effect.

When MLD is indicated in lipolymphedema, it should without exception be combined with consistent compression therapy. Compression therapy is according to the guidelines a firm component of the decongestion and maintenance phase [24]. On economic grounds, too, MLD without compression is irresponsible. The quality and success of MLD depends greatly on the competence of the individual lymphatic therapist. Considerable differences exist here.

**Intermittent pneumatic compression therapy – aim: reduction of edema, reduction of pain**

Intermittent pneumatic compression therapy with multichamber devices can represent a sensible supplement of the therapy spectrum of lipolymphedema in patients with the appropriate compliance, if compression, exercise and MLD do not achieve a sufficient effect. It can be performed by the patients at home after the necessary training [20]. Before prescribing such a device, it is recommended to test the
suitability of the patient for this component of therapy. Some patients with lipedema and extreme pain sensitivity of the tissue find the pressure of intermittent pneumatic compression therapy unpleasant, even at reduced pressure levels. Here, padding with cotton may be helpful [25]. Complications following excessive or inappropriate use can be genital edema or lymph cysts [26].

Liposuction – aim: reduction of mass, reduction of mechanical impairment of walking, reduction of pain, reduction of the tendency to develop hematomas

For several years liposuction has been available as a therapy option for lipedema [27]. In contrast to the above-mentioned conservative measures, it can achieve a reduction of mass. Further, it usually reduces tension, the tendency to develop hematomas and pressure-induced pain of tissue [1, 28]. Unfortunately it is not – as often suggested – capable of curing the disease and eliminating the existing predisposition [20]. The women usually require compression therapy and, if indicated, MLD even after liposuction. Further, after liposuction, weight normalization should be strived for, as otherwise the original state will return after only a few years [29]. The long-term data on liposuction are still weak [1, 28, 30, 31].

The costs for liposuction are 3,000–20,000 €, depending on the degree of intervention; they have to date been reimbursed by the statutory or private health insurances only exceptionally on an individual basis. Reimbursement of the costs is usually only possible if it can clearly be documented by the physician that all conservative measures have been exhausted and that despite this the disease has progressed.

The physician performing liposuction should be selected carefully and possess great experience in liposuction of lipedema. Unfortunately a series of institutions exist that awaken false hopes among women and promise “a cure of lipedema”.

On the basis of data existing to date liposuction in early stages appears to have better outcomes than in advanced cases with decompensation, fibrosis and further consecutive damage [1]. Recent data from a long-term study reveal the greatest profit for patients in stage II–III [28]. Reliable criteria to determine the ideal time for liposuction do not exist.

What is the prognosis of lipedema?

The course of lipedema is usually not predetermined. The course and the severity of findings depend to a large extent on comorbidities such as peripheral arterial occlusive disease, lymphedema, obesity and psychological/psychiatric disorders [32].

With presently available therapy options, cure is not possible, but the patient can positively impact the course by her compliance. Women who consistently wear their compression stockings, exercise and maintain normal weight usually have a distinctly better prognosis and a milder course than those, who in addition to existing lipedema are obese and do not exercise or partake in sporting activity. Decompensation in the sense of lipolymphedema with the ensuing complications also is seen more frequently in women who are obese [1].

Further exacerbating factors are hormonal alterations and pregnancy. This does not imply that women with lipedema cannot or should not become pregnant. During pregnancy, nonetheless, they should continue their lipedema therapy. Compression therapy can be adapted and in the event of additional edema development MLD can be initiated or increased in frequency.

Which differential diagnoses must be considered?

Constitutional variants of normal leg form

During inspection and palpation, the conspicuous criteria of lipedema must be differentiated from constitutional variants of normal leg forms. Often the media suggest an ideal leg form with very thin ankle joints and calves. In reality, the average legs of women, nevertheless, usually appear different. Here, too, a wide range of ethnically-determined leg forms exist. In our experience, women from the Mediterranean region appear more likely to have a tendency to lipohypertrophy of the legs and gluteal region without displaying further signs of lipedema.

Lipohypertrophy in obesity

The most important differentiation from lipedema is lipohypertrophy in obesity [7, 12]. Here, too, there is an increase of volume of adipose tissue, but it affects not only the limbs but also the trunk. BMI is distinctly elevated (≥30 kg/m²) [15], while the waist-hip ratio or the waist-height ratio is abnormal. In extreme obesity, sonography often also reveals lower leg edema because of functional chronic venous insufficiency with all its associated features and complications or even lymphedema [33–35] (Figure 5).

Therapy options here are compression therapy for reduction of edema, but particularly long-term weight loss and exercise. In high-grade obesity this should be accompanied by medical and psychological support, ideally through an obesity center. Simple diets are not suitable. A long-term change of lifestyle and nutritional behavior is required. In case of morbid obesity surgical interventions such as gastric banding or gastric balloon insertion are often necessary.

The measures recommended in the conservative therapy of lipedema are usually experienced as very
pleasant in obesity-induced lipohypertrophy. Through manual lymphatic drainage the sensation of tension in the tissue is also reduced. From the viewpoint of the physician this can be considered as a short-term supplemental measure for moving fluid out of the legs, but it is in no way medically indicated on a long-term basis. The physician’s prescription of MLD in this situation carries the risk of lack of action and compliance of the patient with respect to the urgently needed general measures such as weight loss and exercise.

**Lymphedema**

Lymphedema is often not symmetric. Even though it may occur on more than one limb simultaneously, it is usually not of equal severity in a side-by-side comparison. In contrast to lipedema, in distal lymphedema swelling of the dorsa of the hands/feet is seen and swollen toes/fingers occur. The Stemmer sign (inability to pinch up the skin into a fold on the second toe as an expression of doughy edema) is positive. In a rare proximally-accentuated lymphedema which is usually post-traumatic, particularly after inguinal lymphadenectomy in oncological patients, this sign can be missing. Common to all lymphedema is the possibility of producing dents by pressure as well as the detection of clefts in high-resolution sonography [14]. In lymphoscintigraphy, delayed lymphatic drainage can be found even in early stages [16].

In the event of suddenly manifest lymphedema, age-adapted diagnostic measures to identify the cause of impaired drainage must be undertaken. Every unexplained lymphedema must be considered suspicious for malignancy until proven otherwise [36].

Complex physical drainage and compression therapy with subsequent maintenance is indicated. The initial procedures can be performed on either an outpatient or inpatient basis.

**Phlebedema**

In cases of advanced chronic venous insufficiency (CVI C3–C6), uni- or bilateral leg swelling can occur. The cause can be varicose veins or a postthrombotic syndrome [37] (Figure 6). Additional signs of CVI such as telangiectases,
purpura, hyperpigmentation, atrophie blanche, dermatoliposclerosis and leg ulcers are also seen. The diagnosis can be made using color-coded duplex sonography.

Corrective therapy of the varicose veins is the mainstay of therapy [38]. Depending on findings and comorbidities this can consist of varicose vein surgery, extraluminal valvuloplasty, endoluminal laser or radiowave therapy or sclerotherapy. In case of postthrombotic syndrome, stenting of the occluded pelvic veins should be considered. Otherwise compression therapy with adequately high tension and appropriate pressure for life remains in the forefront.

Rheumatic diseases

Even though lipedema can be associated with pressure-induced and also spontaneous pain, caution is mandated when patients report of severe pain due to compression stockings or even MLD. Typically in lipedema no acute, flaring or immobilizing joint pain occurs. In such patients, an accompanying rheumatic disorder such as fibromyalgia or chronic polyarthritis must be considered.

Patients with corresponding signs and symptoms should be referred to the rheumatologist for further diagnostics and therapy.

Immobility edema

Various conditions can lead to reduced mobility that besides weight gain can cause disproportionate edema. This usually affects patients in wheelchairs, with crutches or rollators who are limited by unilateral paralysis, severe arthrosis, neurological disorders of stiffened joints. Severe edema of the lower leg is seen, initially with normal skin color, in the course with increasing signs of functional chronic venous insufficiency (telangiectases, hyperpigmentation, dermatitis, atrophie blanche, leg ulcer). In case of stiffening of the ankle joint, one also speaks of the arthrogenic stasis syndrome [39].

The aim of therapy here is to restore or improve mobility. Symptomatically medical compression bandages and compression stockings may be employed. When an adequate restoration of mobility is not possible in the long term, intermittent pneumatic compression therapy may also be sensible here. Care must be taken when using compression particularly in patients with neurological deficits and disturbed sensitivity. Here the risk of constriction and erosions is especially great. In such cases prescription of flat-knitted compression stockings at low pressures (class I) is prudent

Conclusions

Only few patients with slowly progressive bilateral leg swelling actually have lipedema. An entire series of differential diagnoses must be considered in these patients. To prevent unnecessary frustrations for patients and therapists as well as unnecessary costs through false treatment, careful diagnostics should be performed and therapy goals be clearly formulated for each individual. True lipedema meeting reliable clinical and sonographic criteria appears to be relatively rare. With simple exclusion criteria, misdiagnoses can be avoided. Nonetheless, there is an urgent need for further criteria for the definitive diagnosis of lipedema.

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