The Lymphedema

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In this chapter, we will look at both the similarities, but mainly the differences between lipedema and lymphedema.

The differences result from the different causes of both diseases. These differences are not always clear to the layperson and are often difficult to understand due to the medically complex interrelationships. It should become clear that, despite some similarities, these are two completely different clinical pictures, which differ significantly from each other in their development, symptoms, diagnosis, and therapy.

However, notwithstanding these differences, the problem is up to now under discussion, and related research is in progress, considering moreover the potentially compromising lymphatic drainage in dysfunctional adipose tissue and the possible, even if relatively rare, evolution of the initial pure lipedema to the lipo-lymphedema state, depending, of course, on lipedema worsening staging.

2.1 Anatomy and Functioning of the Lymphatic System

Our body has two vital transport systems. In addition to our blood circulation, which transports oxygen from the lungs to the tissues and carbon dioxide back, supplies our cells with nutrients and acts as a transport route for hormones, components of blood clotting, and defense, there is a second, almost parallel transport route in our body. This is the so-called lymphatic system (syn. Lymphatic system). While the

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function and structure of the blood circulation are usually well known, the lymphatic system is far less familiar to most people. In the following, we want to change that and give you an understanding of the basic features of the lymphatic system.

As already mentioned, the lymphatic system is also a transport system of our body. On the one hand, it serves to remove fluid from the tissues and thus keep the fluid balance in equilibrium, and on the other hand, it serves as a means of transport for so-called lymphatic substances. These include proteins, fats, bacteria, viruses, and foreign bodies that cannot be absorbed by the capillaries of the blood vessels due to their size. Our lymphatic system is therefore often disparagingly referred to as the "body's garbage disposal system." In addition, the lymphatic system has an indispensable task in immune defense.

To fulfill all these tasks, this unique and highly specialized organ system of our body has a very special structure (Fig. 2.1). On the one hand, it consists of the lymphatic vascular system, on the other hand of the lymphatic organs. The latter, in turn, can be divided into primary and secondary lymphatic organs.

The primary lymphoid organs are responsible for the formation and maturation of progenitor cells into mature immune cells. These include the thymus and bone marrow. The secondary lymphoid organs are where the contact between the mature immune cells and antigens takes place. In addition to the lymph nodes, they include special tissues in the gastrointestinal tract (mucosa-associated lymphoid tissue), the pharynx (pharyngeal, palatine, and lingual tonsils), and the spleen.

Primary Lymphatic Organs

The primary lymphatic organs include the bone marrow, which is located inside all bones, and the thymus, a small gland located in the upper mediastinum. This is where the formation and maturation of special defense cells called lymphocytes or "white blood cells" takes place. The formation of all lymphocytes begins in the bone marrow. Depending on whether their maturation into functional defense cells also takes place in the bone marrow or the thymus gland, a distinction is made between B ("bone marrow") and T ("thymus") lymphocytes. B and T lymphocytes fulfill various tasks of the body's defense system. These include the production of antibodies or the recognition and destruction of viruses or degenerated cells (e.g., cancer cells).

Secondary Lymphatic Organs

Secondary lymphoid organs include the spleen, lymph nodes (Fig. 2.2), and mucosa-associated lymphoid tissue. In these tissues, the so-called antigen presentation and recognition take place. In a sense, the lymphocytes are taught here against which antigens they have to act and how.

The lymphatic vascular system begins with the initial lymphatic vessels, often referred to as lymphatic capillaries or lymphatic collectors. They are the smallest sections and begin as a network between the capillaries of the blood circulation in the intercellular space of organs or the skin. The diameter of such a lymphatic capillary is about 50 μm, which is about 10 times larger than that of a blood capillary. Their task is to absorb tissue fluid and dissolved substances. From here, the lymph

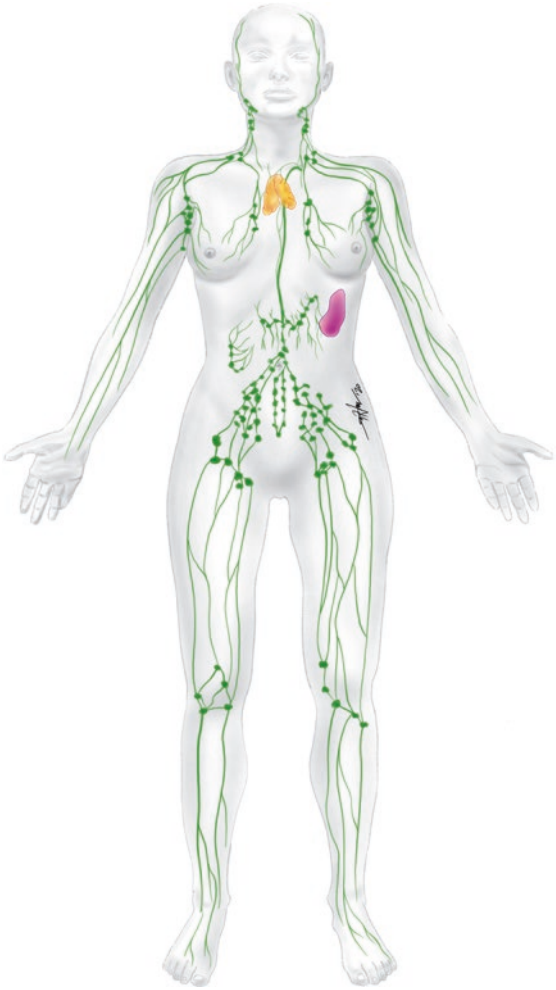

Fig. 2.1 Structure of the lymphatic system

is transported to the larger lymphatic vessels. They are formed by the union of several lymphatic capillaries into so-called precollectors. Several lymph nodes are interposed in these and basically serve as a filtering station. A special feature of the lymphatic vessels is the many interposed valves that facilitate the transport of the lymph and prevent backflow (Fig. 2.3).

Several lymphatic vessels then unite to form the lymphatic trunks, which are usually arranged in pairs. In these lymph trunks, the lymph fluid is collected in each case from a specific region of the body. From here, it is drained into the left and right vein angles via the lymphatic ducts, which form the last section of the lymphatic pathway, and is thus fed into the bloodstream. With the exception of the lymphatic vessels that drain lymph from the right arm and right head and neck region, all lymphatic vessels converge into the main lymphatic trunk (thoracic duct). This eventually drains into the left subclavian vein. Lymph vessels from the right arm and the

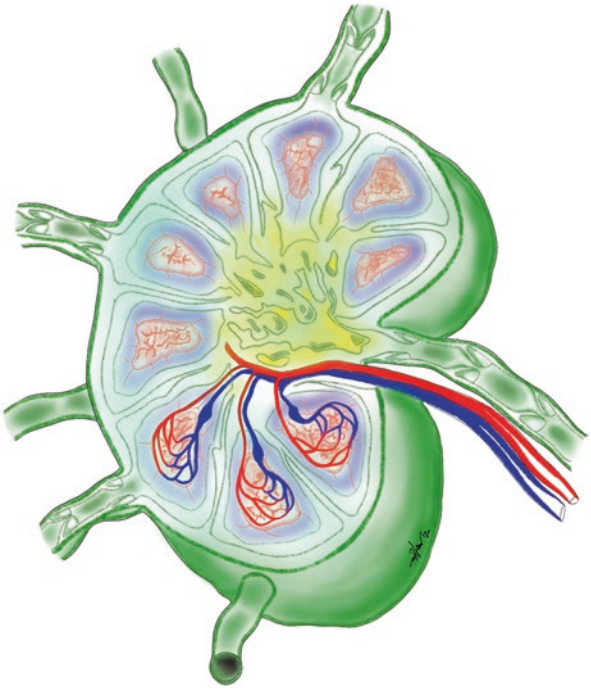

Fig. 2.2 Cross section of a lymph node

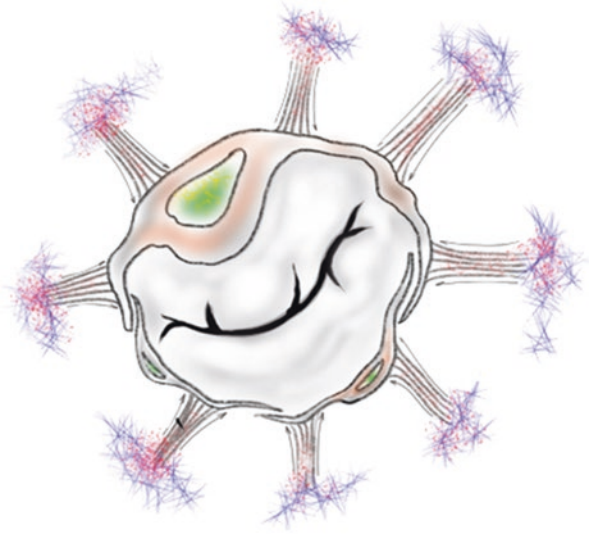

Fig. 2.3 Cross section of a lymphatic valve

right head and neck region, on the other hand, drain into the right lymphatic duct (Ductus lymphaticus dexter), which in turn ends in the right subclavian vein.

Due to this special architecture, the lymphatic system essentially fulfills three different tasks.

Firstly, it acts as a transport system. Every day, approx. 2–3 L of the ultrafiltrated interstitial fluid is reintroduced into the bloodstream. The transport takes place on the one hand passively by contraction of the surrounding skeletal muscles, and on the other hand actively by a peristaltic movement of the muscles built into parts of the lymphatic vessels. The interposed valves prevent the lymph from flowing back (Fig. 2.3).

Secondly, the lymphatic vascular system fulfills an important function in the body's defense system. Through the intermediate lymph nodes, pathogens that can easily penetrate the lymphatic vascular system due to the high permeability of the lymphatic capillaries can be freed. Furthermore, the lymphatic vascular system serves as a transport medium for lymphocytes.

Thirdly, it is the task of the lymphatic vascular system to absorb or transport lipids (fats). Glycerol and fatty acids are absorbed via special lymphatic vessels of the gastrointestinal tract, the so-called chyle vessels, which also have a very high permeability. This allows lipids to be supplied directly to adipose tissue and muscle without first passing through the liver. Due to the high fat content after passage through the digestive tract, the lymph changes its appearance here from clear to milky turbid. In addition to the high fat content, the lymph contains numerous plasma proteins, coagulation factors, and fibrinogen, as well as cellular components (mainly lymphocytes).

Interestingly, the central nervous system is left out of the lymphatic system to protect the brain. This extends from the outside only as far as the meninges. However, there is an indirect connection to the lymphatic system via the brain's own disposal system.

2.2 Causes

Lymphedema is a complex clinical condition. Approximately 140–250 million people worldwide suffer from it. It is caused by a lack of transport capacity of the lymphatic system, which means that the interstitial fluid (tissue fluid between the cells) can no longer be adequately removed, resulting in a backlog of lymph in the intercellular spaces. This appears as a visible and palpable accumulation of fluid, which is accompanied by fibrosis of the tissue (the connective tissue loses its functional properties) and excessive storage of fatty tissue, especially in advanced stages. The lower and upper extremities are most frequently affected. Based on the cause, primary (congenital) is distinguished from secondary (acquired) lymphedema.

Primary Lymphedema/Congenital Lymphedema

Primary lymphedema, which describes the rarer form of lymphedema, is a congenital disorder of the lymphatic vascular system or the lymph nodes, which are either not formed at all or are formed incorrectly.

▶ In primary lymphedema, the lymphatic vascular system is congenitally disturbed.

Most often, there is hypoplasia (lack of formation) of the lymphatic vascular system or a reduced number of lymphatic vessels in a particular region of the body. The lymphatic drainage of the lower extremity is most frequently affected. Less commonly, valvular disorders may also occur. Primary lymphedema occurs sporadically in about 97% of cases and is therefore not inherited. The primary form usually manifests itself with the onset of puberty and can occur unilaterally or bilaterally. Women are affected about twice as often as men.

Secondary Lymphedema/Acquired Lymphedema

This is an acquired damage of the lymphatic system, as a result of which there is a disturbed outflow of the lymph.

▶ Secondary lymphedema is caused by acquired damage to the lymphatic system.

Common causes are accidents, tumor diseases or inflammation of the lymphatic vessels, chronic venous insufficiency (chronic venous congestion), and diabetes mellitus. The most common cause worldwide is lymphatic filariasis, an infectious disease caused by the so-called nematode (*Wuchereria Bancrofti*). In our latitudes, however, this disease plays a minor role. Mostly it is caused by treatments such as surgery, radiation, or the removal of lymph nodes in the course of tumor surgery. The most common example of this is probably secondary lymphedema of the upper extremity (arms) after lymphonodectomy (removal of lymph nodes) from the axilla in breast cancer (Fig. 2.4).

The risk of developing lymphedema of the arm ranges from 9 to 41% in cases of radical lymph node removal and 4–10% in cases where only the sentinel lymph node was removed. Somewhat insidious is the usually delayed onset of lymphedema after surgery; several months to years often elapse. In breast cancer-associated lymphedema, the first symptoms appear on average 8 months after axillary dissection (lymph node removal from the axilla), 75% during the first 3 years. Once onset, the subsequent course of secondary lymphedema is usually highly variable. Some patients may experience only mild, painless, and nonprogressive swelling that does not require therapy, while others may experience rapid progression associated with a severe reduction in quality of life. Unfortunately, if left untreated, the progressive course is the rule rather than the exception.

▶ The incidence for the occurrence of lymphedema of the arm ranges from 9 to 41% in cases of radical lymph node removal and 4–10% in cases where only the sentinel lymph node was removed.

The same applies to the lower extremity as to the upper extremity. Lymphedema can also occur in the head and neck or genital area after lymph node removal. Thus, lymphedema is not limited to the extremities. In addition, there are many reports

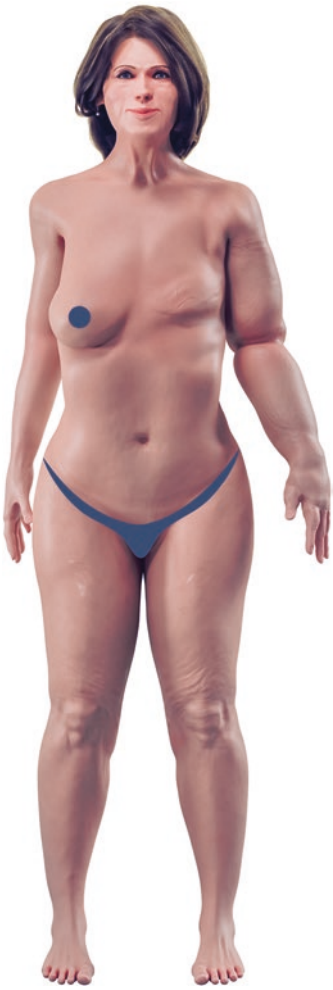

Fig. 2.4 Lymphedema in the area of the left arm after breast cancer

from EBM literature confirming that also secondary lymphedemas related to lymph node removal, often recognize congenital dysfunctional and/or dysplastic latent impairments of the underlined loco-regional lymphatic system.

Malignant lymphedema is a subgroup of secondary lymphedema. In this case, either progressive tumor grows itself or metastasis leads to obstruction of the lymphatic vessels.

2.3 Clinical Appearance

Depending on its expression and classification, lymphedema can be divided, according to the updated ISL Consensus Document, into three different stages (modified by Campisi Staging, 2009), each of which is accompanied by a more or less characteristic appearance.

In the latency stage (stage 0), no symptoms appear yet. It is characterized by reversible, subthreshold edema.

In stage I, a visible and palpable doughy-soft swelling can already be detected. However, this can usually be reversed spontaneously by elevation. Smaller fibrosclerotic tissue changes (changes from functional tissue to connective tissue with a resulting loss of function) may occur in isolated cases.

Stage II is already characterized by marked fibrosclerotic changes and the proliferation of fatty tissue. The palpation changes from formerly doughy-soft to rather hard. At this stage, elevation no longer leads to spontaneous regression. Whereas in stage I, it is still easy to "press in" a dent in the edema area, this is hardly possible in stage II.

Stage III shows the maximum expression of lymphedema. Extensive fibrosclerotic changes and often massive fatty tissue proliferation are evident, which severely restrict natural movement. As edema progresses, the skin tends to develop eczema, erysipelas, or vesicles. Symptomatically, pain, feelings of tension, and a characteristic feeling of heaviness of the affected body part usually occur in the early stages (Fig. 2.5).

2.4 Diagnosis

The medical history is of decisive importance and the first step in the basic diagnosis of lymphedema. Past operations, past infections, tumor diseases as well as vascular diseases or skin changes that may have seemed insignificant up to now, in combination with the corresponding symptoms, already provide initial indications of the presence of lymphedema. A positive family history can also be a further clue.

Furthermore, the assessment of the clinical appearance is elementary, because the external examination can provide information at an early stage as to whether the complaints described are lymphedema or not. In this context, attention is paid to the localization of the swelling and any differences in circumference, which can be just as decisive as the assessment of the skin in terms of color, skin changes, temperature, and texture.

The third decisive step in the initial lymphedema diagnosis is the palpation findings. This is similar to the examination in lipedema. We also check the Stemmer's sign here. It is considered a reliable feature for detecting the presence of lymphedema. However, some caution is required here. A negative Stemmer's sign does not necessarily rule out lymphedema. Palpation also includes the assessment of lymph nodes with their size, consistency, displaceability, and tenderness. Palpation also checks for edema consistency and reliability.

► A negative Stemmer's sign does not rule out lymphedema.

To confirm the diagnosis and to discuss the extent and location of the damage to the lymphatic system in more detail, various other diagnostic procedures can help.

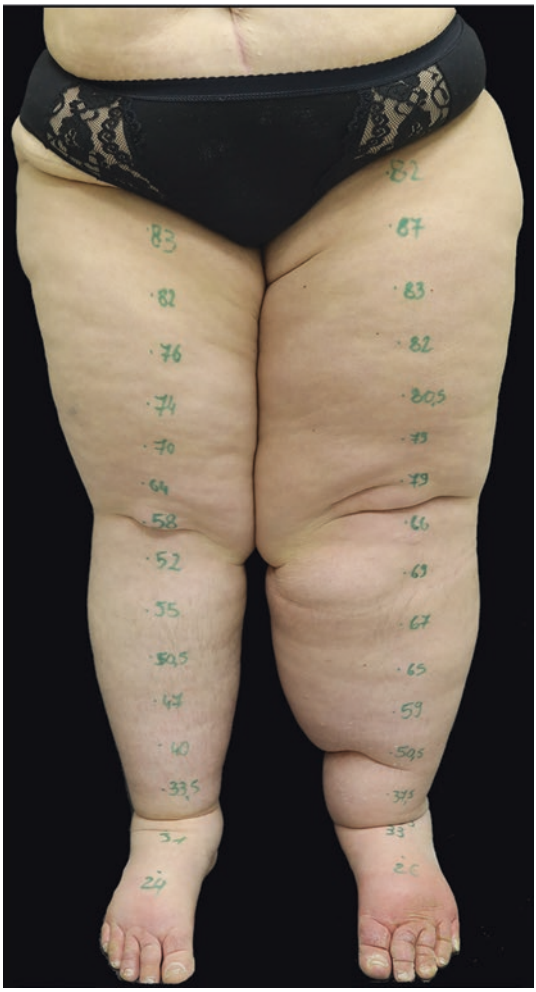

Fig. 2.5 Stage III lymphedema in the left leg after pelvic lymph node removal

Among the imaging procedures, we distinguish morphological from functional diagnostics. Sonography, MRI, and indirect lymphangiography provide information about morphology. Function can be assessed by functional lymph scintigraphy (Campisi et al. 2019; Villa et al. 2019) and fluorescence microlymphography. Indocyanine green lymphangiography (ICG) is also increasingly used.

We perform an apparative diagnosis by means of an indocyanine green lymphangiography. A liquid, fluorescent dye is injected into the patient's skin. This is absorbed by the lymphatic vessels and transported away (Fig. 2.6). The figure shows the cloudy dye injection site in the area between the toes and the good removal of the lymph via the well-illustrated, linear superficial–subdermal lymphatic vessels. The fluorescent dye can be seen and assessed via an infrared camera connected to a monitor (Figs. 2.7 and 2.8) (Campisi et al. 2018; 2020).

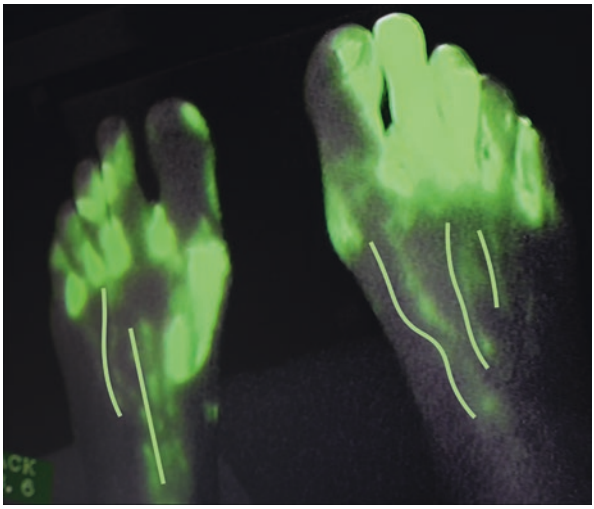

Fig. 2.6 ICG

2.5 Conservative Therapy

Lymphedema is a chronic and usually progressive disease that requires long-term treatment (Fig. 2.9). Therapy includes both conservative and surgical measures and aims to prevent the progression of the disease and alleviate existing symptoms.

Before recommending any therapy, we conduct a medical history survey. Likewise, each patient is thoroughly examined and any additional diagnostics are also performed. Together with the results of the medical history, diagnostics, and examination, we are able to offer patients a treatment plan that is individually tailored to their condition.

The basis of conservative lymphedema therapy is based on a combination therapy of manual lymphatic drainage (MLD), compression therapy, movement exercises, and skin care developed as early as the 1970s. The complex therapy consisting of these four components is summarized under the term "Complex Physical Decongestive Therapy" (CPD). CPD is considered the gold standard and the first-choice therapy for lymphedema.

- CPD (complex physical decongestive therapy) is considered the gold standard and the therapy of the first choice.

Manual Lymphatic Drainage

Manual lymphatic drainage (MLD)is a special form of physiotherapeutic treatment in which the removal of lymph is promoted with targeted hand movements. On the one hand, the accumulation of fluid from the interstitium toward the lymph capillaries is supported in this way, and on the other hand, the self-transport within the lymph vessels is stimulated, which favors the removal of further lymph.

Fig. 2.7 Lymphedema in the area of the arm

In addition to manual lymphatic drainage, appliance-based lymphatic drainage can be performed. Special devices can perform lymphatic drainage at home via an adapted peristaltic compression cuff. There are different providers here, although the devices work according to the same principle. These devices are available from the relevant providers via a prescription after requesting cost coverage from the health insurance company.

Compression Therapy

Compression therapy is also an important component of CPD. The affected part of the body is wrapped with bandages. The pressure applied from the outside supports the drainage of the lymph, and the pressure decreases toward the trunk to ensure a directed lymph flow. For lymphedema, we recommend flat-knit compression garments made to measure, including the hands and feet.

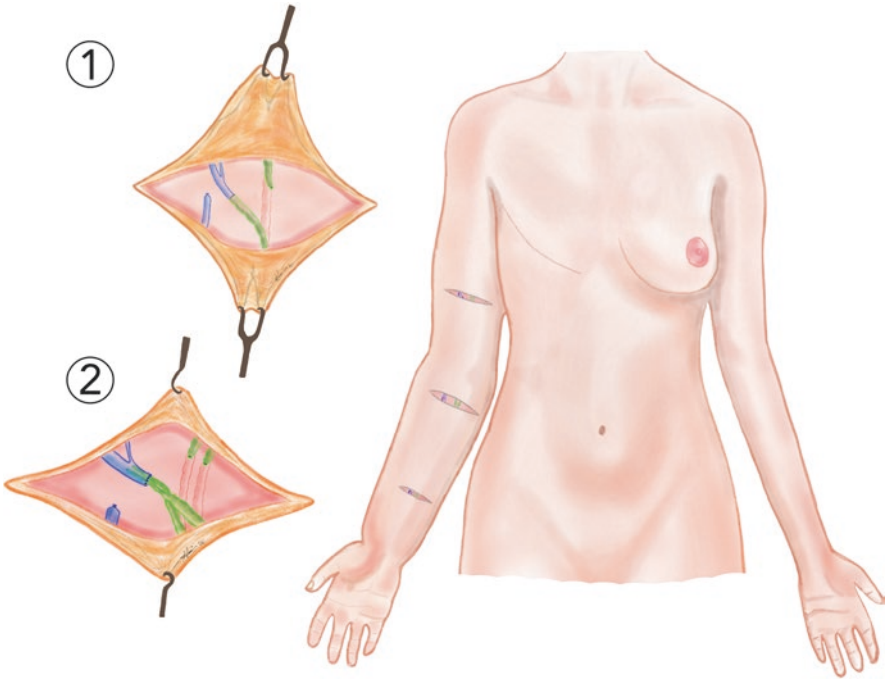

Fig. 2.8 Lymphovenous (1) and multiple lymphovenous anastomosis (2)

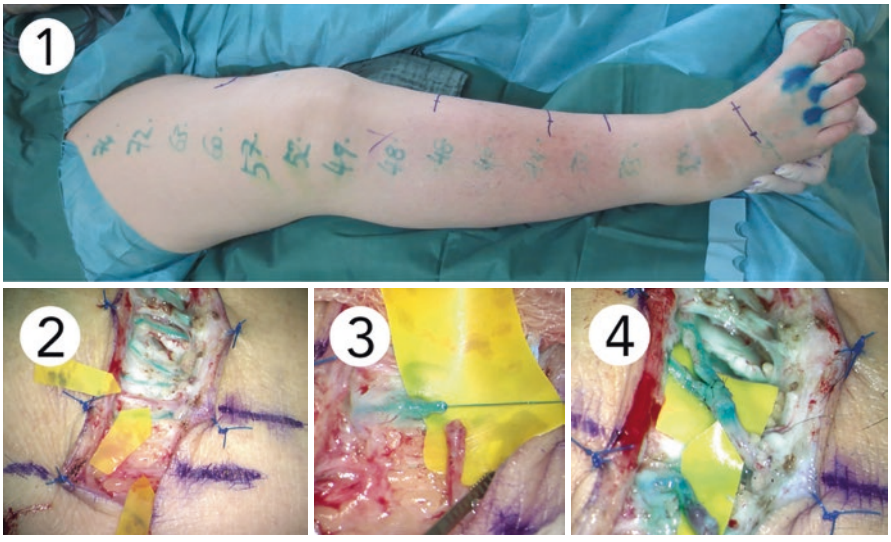

Fig. 2.9 Clinical images of planning and relocation of lymphatic vessels

Movement Exercises
Targeted movement exercises are designed to increase lymph drainage. Among other things, the natural activation of the muscle pump thus promotes passive lymph transport. It is important that an individually tailored therapy program be developed for each affected person.

A new advanced specific protocol is under assessment, in Genoa, named BioCircuit, with tailored exercises by an exclusive Computer Assisted Technology.

Skin Care
Daily skin care is an indispensable pillar of CPD for lymphedema patients. Due to the usually compromised natural skin barrier, the skin is significantly more susceptible to infections. Especially via furrows and rhagades (smallest tears in the skin) germs can penetrate the body and cause severe infections. Bacteria have an easy time spreading due to the defective lymphatic system and poor metabolism in the region.

► For those affected by lymphedema, skin care is essential to prevent serious infections.

CPD is divided into two phases. In the first, so-called decongestion phase, the existing edema is to be reduced as much as possible. In this stage, daily treatments are carried out by means of manual lymphatic drainage, compression therapy by means of wrapping, movement exercises, and skin care. The bandage is worn continuously, except during treatment. Depending on the stage, this phase can last several weeks.

Once the edema has been reduced as much as possible, the maintenance phase begins. The main purpose of this second phase is to maintain or improve the results already achieved. At the beginning of this phase, a flat-knitted compression stocking is fitted. Unlike the circular knitted stocking, this stocking is not stretchable in all directions and therefore provides better compression. In the maintenance phase, the therapy concept also consists of manual lymphatic drainage, compression treatment, movement exercises, and skin care. However, lymphatic drainage usually, in the earliest stages (IB, IIA), no longer has to be performed daily, but from 3 to 4 times a week to 1–2 times every 14 days, depending on the extent. Wrapping, in these cases, is also now only done on the day of therapy. On any other day, the compression stocking can be worn. Often, the initial treatment takes place within the framework of a rehabilitation measure in a clinic specialized for this purpose.

2.6 Surgical Therapy

To understand the therapy of lymphedema, it must be noted that lymphedema is often a chronically progressive disease. It is associated primarily with the sometimes massive accumulation of lymphatic fluid, fibrosclerotic tissue changes, massive fat tissue proliferation, and ultimately also the destruction of lymphatic pathways.

As described above, each patient receives an individual therapy plan. Although often, in advanced stages (IIB, IIIA, and IIIB), a long-term treatment for lymphedema/elephantiasis, CPD has established itself as the gold standard in therapy. The prerequisites for the success of this cure are lifelong implementation and strong compliance on the part of each patient.

If CPD does not achieve the desired success, various surgical options are available in addition to conservative therapy, with the goal of preventing the progression of edema, reducing excessive volume, and improving the aesthetics and function of the affected region.

In principle, a distinction is made between two different approaches. On the one hand, there is the restoration (reconstruction) of lymphatic drainage. This can be achieved, for example, by means of lympho-lymphatic bypasses, lympho-venous anastomoses, performed as lymphatico-venular superficial scattered microanastomoses or as single-site multiple deep and superficial lymphatic-venous anastomoses, or with the so-called vascularized lymph node transfer. Yes, you are right: this sounds complicated, but we will explain these complicated terms in a moment. In contrast, there are resecting (= tissue-removing) procedures that aim purely to reduce mass or volume. These include liposuction and excision (simply cutting away) of the diseased tissue.

Let us first discuss the reconstructive options for lymphedema treatment. In these surgical measures, we distinguish techniques,

- based on surgical treatment of the lymphatic vessels,
- transplant the lymph nodes, and,
- which aim to resprout lymphatic vessels.

2.6.1 Restorative/Reconstructive Surgery

Advances in the field of surgery have now made it possible to identify microscopic lymphatic vessels and assess their quality during surgery. This opens up the possibility of at least partially restoring impaired lymphatic drainage. We would like to explain various techniques to you below.

Lympholymphatic Bypass

This technique can be used, in selected cases, to bridge individual sections with restricted lymphatic drainage. For this purpose, an endogenous lymphatic vessel (or vein) is removed from a region of the body not affected by lymphatic drainage. This lymphatic vessel is then connected to functional sections of the lymphatic vessel system both far from the body and close to the body of the drainage disturbance. The lower the stage of lymphedema, the more promising this technique is. Individual studies have demonstrated up to 80% reduction in the circumference of the affected limb. A disadvantage is that in isolated cases lymphedema may occur in the region of the removed lymphatic vessel.

Lymphovenous Anastomoses

These methods represent today the most frequent microsurgical techniques applied in clinical practice for lymphedema treatment.

A direct connection between the lymphatic system and venous circulation is also established here. The advantage over lymphovenous bypass is that the removal of a donor vessel can be dispensed with. In fact, with this technique, lymphatic vessels are connected to smaller veins in the immediate vicinity. Individual studies describe a subjective improvement in symptoms in up to 95% of patients after such an intervention. The great advantage of this scar-saving technique is the comparatively less traumatic procedure, which significantly reduces the perioperative risk. In isolated cases, wound healing disorders or the formation of lymphatic fistulas may occur.

The figure (Fig. 2.11) schematically shows a (1) lymphovenous anastomosis (LVA) and (2) multiple lymphovenous anastomosis (MLVA). The difference between LVA and MLVA is that in MLVA, a single lymphatic vessel is not connected 1:1 with a vein, but several lymphatic vessels are inverted into a vein and connected. In Campisi's experience single-site MLVA is performed at the inguinal crural region for lower limb lymphedema, and at third medium-superior of the volar surface of the arm for upper limb lymphedema. In addition, Campisi does not use a cross skin incision along the limb, except to approach the inguinal crural region.

Figure 2.9 shows a lymphedema patient in our operating room. Images 2–4 were taken with 50x microscope magnification. Lymphatic vessels were visualized via injection of indocyanine green (1). Subsequently, the lymphatic vessels and veins were visualized. The yellow plastic arrows point to the veins, and the blue–green colored vessels are the lymphatic vessels that absorbed the dye from the tissue (2). For a lymphatic vessel to be sutured, we (Jandali–Jigas's Technique) cannulate it with a hair-thin thread (3). In picture (4) the completed detour of the lymphatic vessels into veins can be seen.

Vascularized Lymph Node Transplantation

One of the newer techniques of lymphedema therapy is free vascularized lymph node transfer (Fig. 2.10). The principle is the removal of a lymph node package, including its vascularization, from an unaffected part of the patient's own body and the transplantation of this package into the area of lymphedema. In theory, two different mechanisms triggered by this procedure are thought to improve lymphatic drainage. Firstly, the transplanted lymph nodes act as a kind of sponge, so to speak, sucking up the lymph in the region and directing it toward the lymphatic vessel. On the other hand, the lymph node transplantation results in a new lymph vessel sprouting in the area surrounding the lymph node. The newly formed lymphatic vessels then carry the lymph to the lymph node, and from there, further, metabolization occurs via the vein of the lymph node into the venous circulation. Several body regions can be used as donor sites. The groin region, the chin, and neck area or the area above the collarbone and lymph nodes from the abdominal cavity have become established. We most frequently remove lymph nodes from the abdomen, as the risk of suffering lymphedema as a result of the removal is significantly reduced in this area.

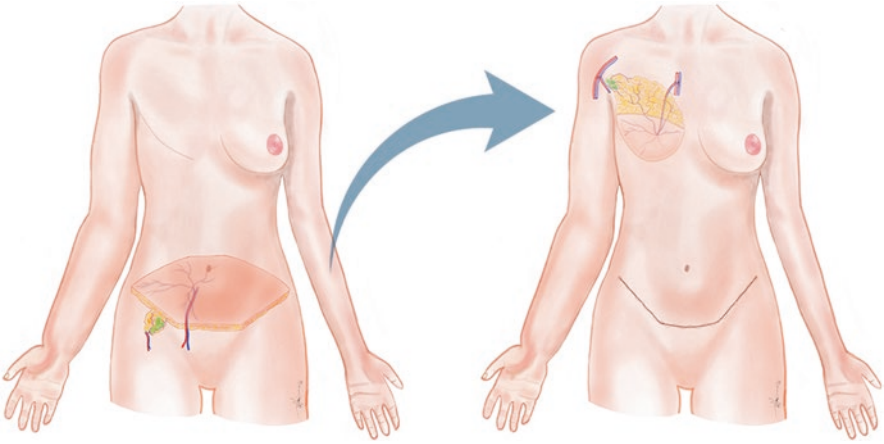

Fig. 2.10 Clinical images of planning and relocation of lymphatic vessels

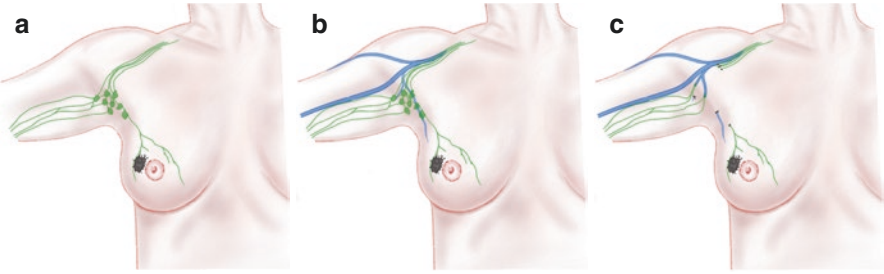

Fig. 2.11 The LYMPHA principle

However, research is in progress to establish the potential risk of malignant degeneration in the transfer site, reported in some recent articles, due to the growth factors locally induced by lymph node transfer on the immune altered lymphedematous tissue, with lymphangiosarcoma (like Stewart–Treves Syndrome) or carcinoma frightful implant. That is why, on the ethical, deontological, and medicolegal points of view, this terrific event, even if exceptional, would be considered and clearly explained to the patient, acquiring his/her informed consensus.

Das LYMPHA-Prinzip (Lymphatic Microsurgery Preventive Healing Approach)

An example of lymphedema treatment that we perform very frequently is the combined treatment of breast reconstruction after breast removal and lymphedema treatment after lymph node removal from the armpit. For breast reconstruction, the transfer of excess skin-fat tissue from the abdomen is performed. In addition, a lymph node package is relocated from the groin to the armpit. Finally, the removed tissue is connected to the local blood supply in the recipient area.

Due to the anatomy of the upper extremity lymphatic drainage, lymphedema often develops on the arm of the affected side after breast removal in combination with lymph node removal. The removal of multiple lymph nodes in combination with the injury to multiple lymph vessels from surgery can be compensated for to some degree, but are also eventually exhausted.

Due to the progress in the field of microsurgery in the course of the last years, it is nowadays possible for us to identify these damaged lymphatic vessels and to restore them immediately. On the one hand, this can be done by directly suturing the injured lymph vessels or by connecting the lymph vessel to a vein in the surrounding area.

In practical terms, this means that a trained plastic surgeon joins the operation during the lymph node removal from the armpit and diverts the injured lymph vessels directly into veins (i.e., as a precaution). This extends the total operation time by 30 min and requires good cooperation between oncological and plastic surgery teams. Studies have shown that this significantly reduces the risk of lymphedema.

In Fig. 2.11, we show the principle of LYMPHA operation. (A) Before tumor removal. The dark dot above the nipple represents the tumor, green the lymphatic vessels. (B) As (A), but with veins. (C) After tumor and lymph node removal and redirection of lymph vessels into draining veins.

2.6.2 Tissue Removal Measures

Liposuction

We will discuss liposuction in detail in Chap. 3, Treatment of lipedema. Its primary purpose is to reduce the increase in subcutaneous fatty tissue observed in advanced lymphedema. Although it primarily leads to a reduction in circumference and an associated improvement in function and aesthetics of the affected limb, studies also show a marked improvement in lymphatic drainage after surgery. There appear to be several explanations for this: First, tissue injury during surgery could result in connections between lymphatic vessels and veins, allowing lymph to be delivered directly to the bloodstream. On the other hand, injuries to the respective muscle fasciae could promote drainage of the lymph from the superficial to the deep lymphatic vascular system, which actually makes more sense.

In summary, liposuction for the treatment of lymphedema is a comparatively low-risk procedure, only if performed by lymph vessel sparing procedure, on the guide of the fluorescent ICG microlymphography. In this way, the risk of aggravating lymphedema during surgery by injuring remaining, functional lymphatic vessels is quite low if the technique is correctly adopted. On the contrary, if liposuction is performed without this kind of lymph vessel procedure, due to the total lymph vessel debulking, the consequent heavy charge is the permanent and mandatorily need to continue wearing compression garments for the rest of the patient's life. Then, debulking blind liposuction is not a measure that restores lymphatic drainage, and therefore is more likely to be noted as a fallback option. In Campisi's experience, as a matter of fact, lymph vessel sparing selective liposuction (by this author

preferably named fibro-lipo-lymph-aspiration, to avoid any possible confusion with the blind liposuction) is regularly performed as a sequential complementary therapeutic procedure, after MLVA microsurgery, for the effective treatment of advanced lymphedema.

In any case, plastic surgeons today have to be very careful in applying liposuction, even if for only aesthetic indications, and have to be skilled to respect lymph vessels during this procedure.

Overall, the pre- and postoperative care, as well as the surgical procedure, differs from liposuction for lipedema. For example, before surgery, the edema must be minimized as best as possible. Likewise, compression must be worn much more consistently after surgery.

To be updated on this topic concerning relationships between lymphatics and lipedema, both on theoretic and on practical points of view, it is mandatory to explain that, although assuming the specific differences between lipedema, lymphedema, and the relatively rare lipo-lymphedema, there are recent review articles in which is underlined that "expanding adipocytes produce some lymphangiogenic factors, such as VEGFC, which may induce lymphatic hyperplasia. Lastly, in hypoxic environments, hypoxia-inducible factor 1 enhances fibrosis, thus potentially compromising lymphatic drainage in dysfunctional adipose tissue. Taking into account these findings, research is still needed to clarify whether a persistent and progressive damage of the microlymphatic vessels because of adipose tissue expansion, rather than a primary lymphatic defect, may be responsible for the lipo-lymphedema state" (Buso, Mazzolai et al., Obesity, 2019: 27, 10, 1567–1576).

In Campisi's recent experience there is an exemplary case of a lipedema, initially diagnosed by other specialists as a pure lipedema, in which superficial and deep lymphoscintigraphy, according to the Genoa protocol (with the additional calculation of the transport index), showed a latent functional and clinical impairment of the lymphatic circulation, allowing us to perform the proper tailored treatment by MLVA at the inguinal crural region.

To conclude, approaching lipedema surgery, the skilled plastic surgeon must be sure that the lymphatic system is functionally intact and, in any case, it has to be respected during the surgical procedure.

Tissue Removal/Debridement (Charles Procedure)

Radical removal of the areas affected by lymphedema (skin and subcutaneous tissue) is nowadays reserved exclusively for the most severe forms of lymphedema. The aim of this technique is to remove the skin with all underlying fatty tissue down to the respective muscle skin and then cover it with a skin graft. However, the improved function of this procedure is offset by the unsightly result and the high surgical risk (Fig. 2.12).

If it were now a matter of explaining how we make our decision as to when to use which procedure, it would go a little too far. If surgical reconstruction is indicated,

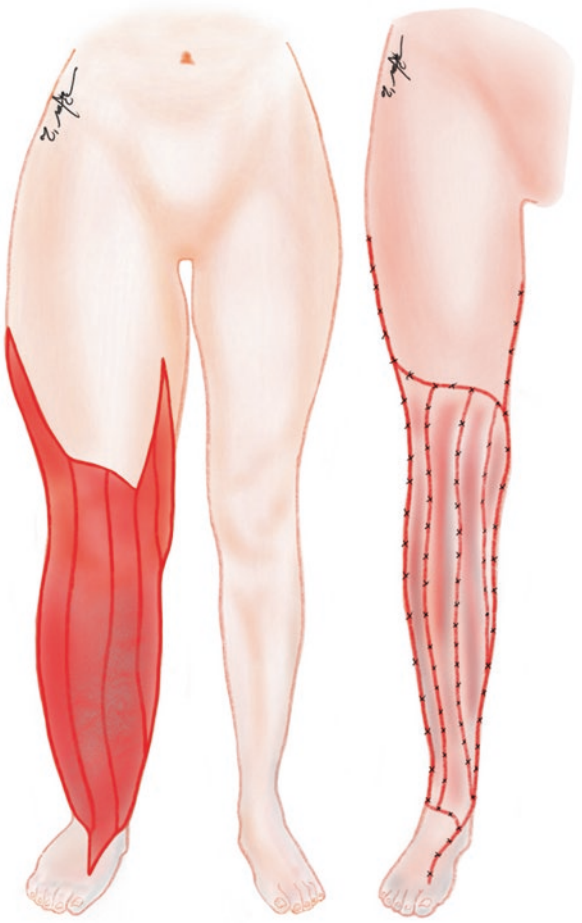

Fig. 2.12 Principle of the Charles operation

we make our decision based on the individual lymphatic vessel status and the overall medical history. Currently, according to Jandali's procedure, lymph node transplants are most frequently performed, followed by lymphovenous "shorts", obtaining better results with lymph node transplantation than with lymphovenous detour. In Jandali's experience, the majority of cases (except for lymphedema following axillary lymph node removal after breast cancer), is treated by harvesting lymph node packages from the gastric region. The removal is performed laparoscopically through only three small incisions. The subsequent transplantation usually takes place quite quickly within 2–4 h.

According to Campisi's experience, the majority of cases is treated by MLVA (alone, in the stages I A-B and II A), and followed by sequential fibro-lipo-lymph-aspiration with lymph vessel sparing procedure for stages II B, III A–B.

2.7 Similarities and Differences of Lipedema and Lymphedema

It is not uncommon for lipedema to be referred to as lymphedema or other diseases or to be confused with them. As explained in detail in the previous sections, these are fundamentally different clinical pictures whose causes, diagnostic possibilities, and therapies largely differ greatly from one another.

Gender Distribution
Let's first take a look at the gender distribution of the two diseases. This is where we see the most obvious difference in our daily clinical routine. Lipedema manifests itself almost exclusively in women. The cause of this remains unknown, despite increasing research in this area. Hormonal influences are considered to be the decisive factor. The frequent onset in phases of hormonal change, such as puberty, as well as the aggravation during pregnancy or even the late onset during menopause, speak in favor of this. If lipedema occurs in men, it is usually associated with other diseases (e.g., cirrhosis of the liver, hypogonadism) or is a side effect of hormonally active therapies (e.g., therapy of prostate carcinoma). Lymphedema, on the other hand, affects both men and women.

Cause
In contrast to lipedema, lymphedema has a tangible cause, namely either congenital (primary) or acquired (secondary) damage to the lymphatic transport system. This damage can, of course, vary greatly in its origin and severity. It should be noted that lymphedema (at least primary lymphedema) also occurs much more frequently in women than in men. Both diseases show a familial accumulation.

- Lipedema occurs almost exclusively in women, while lymphedema occurs in both men and women.

Affected Areas
A further difference can be seen in the external appearance of both clinical pictures. Although lipedema and lymphedema may look the same at first glance, since they share the symptom of swollen legs, ultimately a closer look at the affected areas usually reveals clear differences. While the swelling in lipedema always affects both legs or both arms, in lymphedema often only one leg or arm is affected by the increase in circumference. If in rare cases of lymphedema, swelling occurs on both sides, one side is usually more affected than the other. Feet and hands also show a clear difference in both clinical pictures. While the feet and hands are excluded from the swelling in lipedema, the backs of the feet and hands are usually clearly swollen in lymphedema (Fig. 2.13). This can be verified by a positive Stemmer's sign.

On the surface, lipedema is often accompanied by obesity, which places an increasing burden on those affected. Lymphedema, on the other hand, usually occurs independently of obesity, at least in the early stages.

Fig. 2.13 Swollen back of the hand in lymphedema

Palpation

During a closer examination in the course of our clinical examination, clear differences in the palpation findings of both diseases can also be observed. Lipedema appears mostly soft, often described as doughy or spongy. When the tissue is pressed in, no dent remains.

The tissue is similarly soft in early stages of lymphedema (stages 1 and 2). If we press the soft edema in lymphedema, a visible dent remains. In advanced lymphedema, where longer term edema deposits lead to increased collagen formation and thus to hardening of the tissue, pressing in is no longer possible.

Consequently, dents can only be depressed in "soft" lymphedema (early stages), but not in "soft" lipedema. In the late stages of lymphedema, the tissue is too hard to be depressed.

Skin Lesions

Further differences can be seen when looking at the skin of lipedema and lymphedema. The externally visible skin changes in lipedema are caused by the proliferation of fatty tissue under the skin without any actual structural change in the skin structure. In the early stages, the skin appears finely knotty, while a more coarse-knotty appearance occurs in later stages.

In lymphedema, on the other hand, the protein-rich edema in advanced stages leads to structural changes in the skin and subcutis. Initially, there is a thickening of both the subcutis (i.e., the lower skin) and the cutis (skin), which is caused on the one hand by an increase in the subcutaneous fatty tissue and on the other hand by an increase in the connective tissue. Furthermore, trophic changes occur in the uppermost skin layer, the epidermis. The changes range from dry skin to hyperkeratosis, excessive growth of the uppermost skin layer, the already described hardening (pachyderma), often also called elephant skin, to the formation of areal skin tumors (papillomatosis), lymphatic vesicles, and ulcers.

Ultimately, the aforementioned skin changes in lymphedema, in combination with the impaired removal of lymphatic fluid, lead to damage to the natural skin barrier, which results in a significantly higher incidence of infections (e.g., erysipelas or cellulitis) in lymphedema than in lipedema.

Complaints

Let us now take a closer look at the complaints of both clinical pictures described by those affected. Here too, in addition to a few similarities, there are major

differences between lipedema and lymphedema. It should be mentioned that the symptoms listed below represent only a cross section of the symptoms described by those affected. The occurrence is sometimes subject to strong individual variations.

Having said this, let's start with the similarities: First of all, what both diseases have in common is that the symptoms that occur significantly restrict the quality of life in everyday life and at work. For example, the increase in circumference can lead to restricted movement, which occurs in advanced stages of both diseases and is not infrequently so severe that the natural gait pattern appears to be significantly impeded.

In the case of lipedema, pain clearly dominates the symptoms of most of those affected. It should be clarified here that the currently valid staging does not take into account the painfulness of this disease. As a result, there is no direct correlation between stage and pain. This means that patients with stage I lipedema can subjectively experience significantly more pain than, for example, patients with stage III lipedema, but the same is also true the other way around—we have already discussed this topic several times in this context. Pain is described much less frequently in lymphedema and is more likely to occur in advanced stages or the case of complications such as erysipelas or cellulitis. The everyday limitations of lymphedema are mostly caused by the sensation of tension and heaviness.

Those affected by lipedema often report a strong sensitivity to touch, which is described rather rarely in lymphedema. The tendency to hematoma formation after minor trauma is also more likely to be attributed to lipedema than to lymphedema.

Apart from the obvious symptoms, sufferers of both conditions have to contend with severe restrictions in their everyday lives. For example, the usually one-sided swelling of lymphedema causes unexpected problems when buying clothes. Pants or tops usually have to be purchased several sizes too large to accommodate the one-sided swelling. Furthermore, the clothing often constricts the skin, which often causes problems due to the poor quality of the skin.

► In lipedema, the pain usually dominates the symptoms. These occur regardless of the respective stage. In lymphedema, these are usually only found in advanced stages.

Objectivity

Another striking difference is the objectifiability of both diseases. The basic diagnostic procedure, which is the same for both diseases and consists of anamnesis (questioning), inspection (examination) and palpation (palpation), allows the trained and experienced examiner to draw clear conclusions about the clinical picture. The distinction between lipedema and lymphedema seems to be relatively easy to make. But what about the distinction between lipohypertrophy and lipedema, whose only difference is the painfulness of the affected areas in lipedema? In this case, the examiner is solely dependent on the description of the affected person and can only make the diagnosis on the basis of his experience, examination, and statements of the affected person. Further diagnostics are simply not available when diagnosing lipedema. Unfortunately, the disease cannot be objectified in comparison to lymphedema, which makes it difficult for it to be recognized as a health insurance benefit. In the

case of lymphedema, on the other hand, we have numerous, so-called advanced diagnostic procedures at our disposal. In addition to morphological imaging procedures (MRI, CT, and ultrasound), these also include functional diagnostics (functional lymphoscintigraphy, indocyanine green lymphography) and various genetic tests.

▶ Lymphedema is objectifiable as a disease, lipedema is not.

Treatment

Although we will discuss therapy, especially that for lipedema, in detail in subsequent chapters, we will briefly discuss similarities and differences in both conditions.

Despite the commonality of CPE as a conservative therapeutic approach, it must again be made clear that lipedema and lymphedema are completely different clinical pictures. This is also the reason for the different therapy.

In lipedema, CPE only leads to an improvement of symptoms in some cases; a complete alleviation of symptoms by the combination of compression and lymphatic drainage is almost impossible. Particularly with regard to manual lymphatic drainage in lipedema, there is no proven effect. The only remaining therapeutic approach is liposuction, which, in our experience, greatly alleviates or completely eliminates the symptoms in almost all patients. It should be noted that even if the symptoms are completely reduced after surgical treatment of lipedema, it cannot be said that the disease has been cured. Also, a recurrence of the disease cannot be excluded by surgical therapy. The disease is therefore not curable.

In principle, CPD can achieve a significant improvement in the symptoms of lymphedema. In contrast to lipedema, manual lymphatic drainage represents a central point of therapy. It is also important to distinguish between congenital and acquired lymphedema. In addition to CPD, we now have numerous microsurgical procedures at our disposal, which can increasingly lead to a complete and, above all, permanent reduction in symptoms and even cure.

The differences between lipedema and lymphedema are shown in Fig. 2.14.

We do not want to leave unmentioned that there are also mixed pictures of these diseases among themselves or with other diseases. Lipo-lymphoedema and phlebolymphoedema should be mentioned in particular. We have already discussed obesity.

As the name suggests, lipolymphedema is a mixed form of lipedema and lymphedema. In some patients, lymphedema also develops during the course of lipedema (Fig. 2.15). In addition to the typical symptoms of lipedema, there are also symptoms of lymphedema that are not usually found in lipedema. An example of this is the swollen backs of the feet or hands or edema on the lower legs that can be pushed away. In contrast to pure lymphedema, the edema in lipo-lymphedema is usually symmetrical.

In Fig. 2.16 marked lipo-lymphoedema after massive weight loss is shown.

Phlebo-lymphedema is a combination of venous disease and lymphedema. It is caused by chronic venous insufficiency, a venous outflow obstruction that can be caused, for example, by varicose veins, phlebothrombosis, or arteriovenous malformations. This damage to the veins can result in the blood not returning properly from the periphery of the body back to the heart. The blood backs up, so to speak, and presses fluid out of the veins into the surrounding tissue.

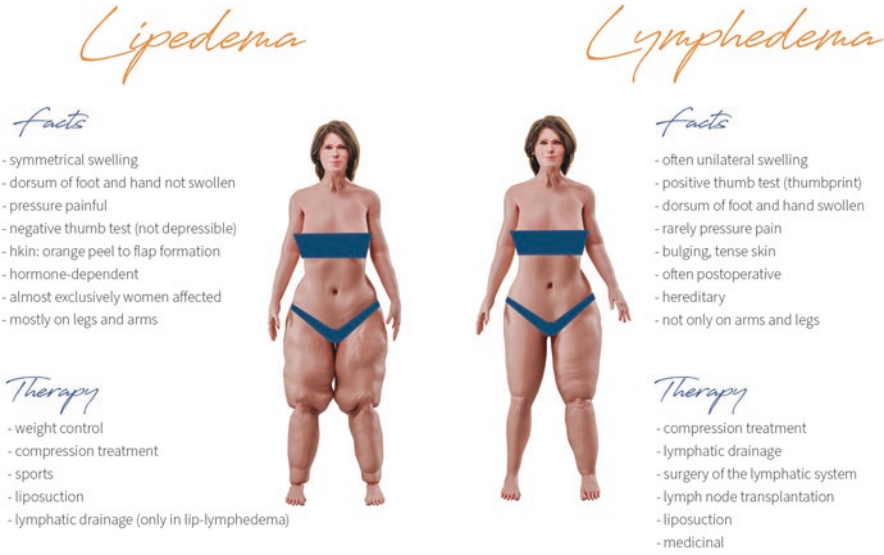

Fig. 2.14 Differences between lipedema and lymphedema

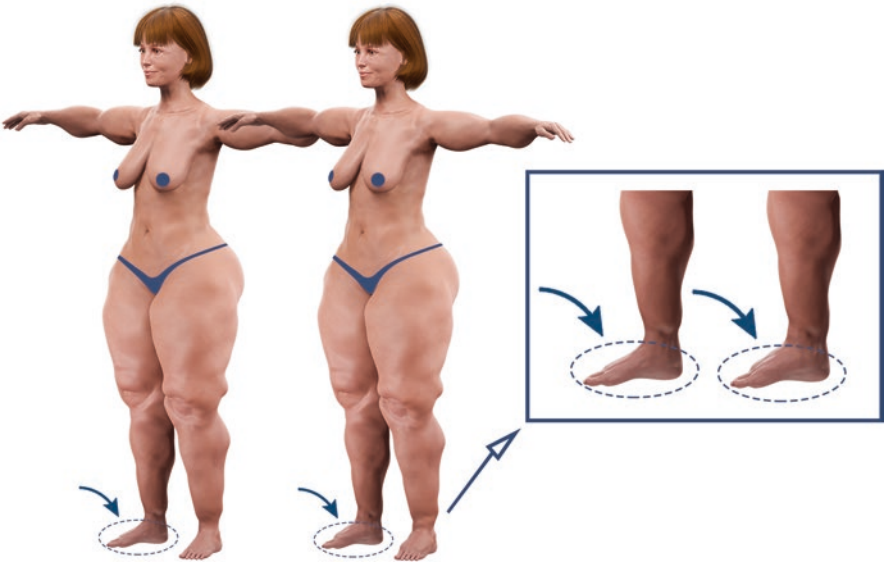

Fig. 2.15 Dorsal edema of the foot in lymphedema

As a consequence, increased tissue fluid is produced here as well, which—similar to lipo-lymphoedema—leads to an overload of the lymphatic vascular system. In phlebo-lymphoedema, too, early treatment of the underlying disease is indispensable. Manual lymphatic drainage and compression therapy are prescribed as supportive measures.

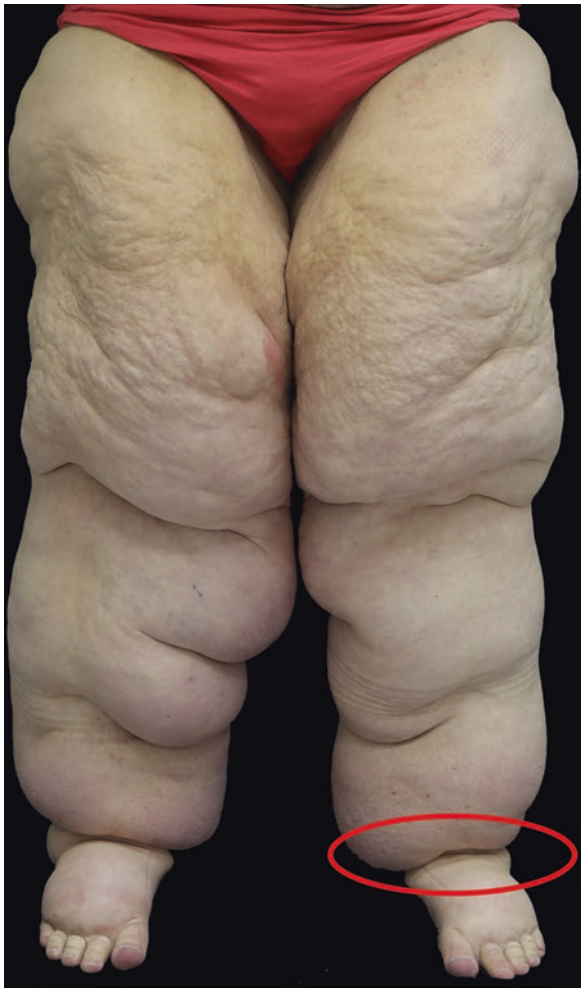

Fig. 2.16 Lipo-lymphedema after massive weight loss

There is another very impressive observation from our daily surgical routine when we compare lipedema and lymphedema. When we take a patient with lymphedema to the operating room and make a skin incision, tissue water (edema) escapes from the wound immediately after penetration of the skin with the scalpel. Occasionally, this edema discharge can be observed through the skin suture into the dressing for several days after the operation. The situation is completely different in lipedema. Although a small incision must be made through the skin at the beginning of every liposuction procedure, we have never seen even a drop of tissue water leak out in lipedema in the past 15 years.

Basic differences and similarities between lipedema and lymphedema are summarized here.

1. Lipedema and lymphedema are two entirely different conditions, both of which cause swollen legs.

2. Lipedema occurs almost exclusively in women, while lymphedema occurs in both men and women.
3. Lipedema always shows a symmetrical swelling. Lymphedema often shows asymmetric swelling of an arm or leg.
4. In lymphedema, the backs of the hands and/or feet are also affected by swelling, but not lipedema.
5. Stemmer's sign is negative in lipedema but positive in lymphedema.
6. The swelling in lipedema feels soft, in advanced lymphedema, it is hard and bulging.
7. In lipedema, the pain usually dominates the symptoms. It occurs regardless of the respective stage. In lymphedema, pain is usually observed only in advanced stages.
8. Common complications of advanced lymphedema are erysipelas (erysipelas) and cellulitis. These do not usually occur in lipedema.
9. A tendency to hematoma formation is observed in lipedema, even after minor trauma, but not in lymphedema.
10. Lymphedema is caused by a disorder of the lymphatic transport system. The cause of the development of lipedema is not clear to date.
11. Obesity can lead to the development of lymphedema. In lipedema, it can have a negative effect on progression and also be associated with it.
12. Lymphedema can usually be diagnosed causally with diagnostic imaging procedures. There is no apparative examination that is conclusive for lipedema.
13. Both diseases may or may not progress. Whether in what time frame or to what extent the diseases progress cannot be predicted for both lipedema and lymphedema.
14. Manual lymphatic drainage is a core element of lymphedema therapy. In lipedema, it usually has no lasting effect.
15. In both diseases, it is important to treat not only the physical effects but also the psychological stress.

References

Campisi CC, Villa G et al (2019) Rationale for the study of the deep subfascial lymphatic vessels during lymphoscintigraphy for the diagnosis of peripheral lymphedema. Clin Nucl Med 44:91–98

Campisi C, Ryan M, Campisi CS, Boccardo F, Campisi CC (2018) Lymphatic Venous Anastomosis Applied in the Surgical Management of Peripheral Lymphedema: from Prophylaxis to Advanced Disease. In H-C Chen, P Ciudad, S-H Chen, YB Tang. Lymphedema Surgical Approaches and Specific Topics (Chapter 6, pp. 55–70). Elsevier. 2nd edition

Campisi C, Marlys W et al (2020) Matching Primary with Secondary Lymphedemas across Lymphatic Surgery in Genoa Italy from 1973 until time of Covid 19. Italian Journal of Vascular and Endovascular Surgery, Minerva Medica 2021(March);28(1):25–41.

Villa G, Campisi CC, Campisi C et al (2019) Procedural recommendations for lymphoscintigraphy in the diagnosis of peripheral lymphedema: the Genoa Protocol. Nuclear Medicine and Molecular Imaging 53:47–56