

## REVIEW SECTION

# Update in the management of lipedema

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### ABSTRACT

**Introduction:** Lipedema is a chronic feminine disease that causes abnormal fat deposition in lower limbs and occasionally upper limbs. Easy bruising and pain are common. Lipedema patients suffer from both physical and psychological disability. Despite the relatively high prevalence and the impact on the quality of life, little is known about the disease. Most patients are misdiagnosed as lymphedema or obesity. The aim was to perform a non-systematic review on lipedema literature, related to diagnosis and therapy.

**Evidence acquisition:** A literature search was performed by three researchers, to retrieve pertinent articles in PubMed<sup>5</sup> Web of Science<sup>6</sup> and ResearchGate<sup>7</sup> from the last 20 years. The documents were selected from systematic reviews, reviews, meta-analyses, consensus documents and guidelines, randomized controlled trials and retrospective, cohort and clinical series.

**Evidence synthesis:** Regarding pathophysiology, alterations are not exclusively confined to adipose tissue. Lymphatic dysfunction, cardiovascular variations, blood capillary fragility and increased permeability are common. Patients often present with neurological alterations and hormonal malfunction. Elevated cutaneous sodium has been documented. Due to the absence of a defined etiology, evidence-based research is difficult in the management of lipedema.

**Conclusions:** The setting of realistic expectations is important for both patient and medical care provider. The major aims of the management are multimodal for improvements in the quality of life; reduction in heaviness and pain, reshaping the affected limbs, weight control, improvements in mobility. Compression garments, physical therapy, exercise regimens, diet and psychological counseling are necessities. For selected patients, surgical treatment is an added option.

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**Key words:** Lipedema; Obesity; Lymphedema; Lymphatic Irradiation; Lipectomy.

## Introduction

### Importance of the topic

**L**ipedema is a chronic disease that it has been reported to in 11% of the female population, with a real prevalence potentially higher considering the frequent underdiagnosis. It causes an abnormal fat deposition in their lower limbs, easy bruising and pain.<sup>1</sup>

Patients complain of swelling that often begins during puberty. This swelling is disproportionate between the upper and the lower part of the body with obvious enlargement of the hips and lower extremities. These classic physical signs increase dramatically with weight gain. This condition results in remarkable physical and psychological disability.

Despite the increasing research in this disease and awareness among health professionals, its inclusion as a MESH term in Medline is recent. In 2018, upon request by the European Society of Lymphology, it was included as a condition in the International Classification of Diseases (ICD) by the World Health Organization as “EF02 Certain noninflammatory disorders of subcutaneous fat.”<sup>2</sup> Even though little is known about lipedema, its high management costs and low curative rate, its inclusion in the ICD is expected to further encourage research efforts. In fact, new management guidelines have been published in the last years.<sup>3</sup> It is necessary to increase awareness to help patients in facilitating an early and precise diagnosis and an accurate management.<sup>4</sup>

The objective of this article was to perform a non-systematic review of the literature on lipedema, its diagnostic criteria and proposed treatments.

### Evidence acquisition

#### Methodology

We performed a narrative review of publications inherent to lipedema. A literature search was performed by three researchers, to retrieve pertinent articles in PubMed<sup>5</sup> Web of Science<sup>6</sup> and ResearchGate<sup>7</sup> from the last 20 years. The documents were selected from systematic reviews, reviews, meta-analyses, consensus documents and guidelines, randomized controlled trials and retrospective, cohort and clinical series. The MesH was lipedema and we included 91 relevant papers.

### Evidence synthesis

#### Epidemiology

Although the lack of epidemiologic studies to measure the real prevalence of lipedema among populations, lipedema is estimated to affect 0.06% to 11%.<sup>1, 8</sup>

Only a few studies are available worldwide:

- Földi: prevalence of 11% in women;<sup>1</sup>
- Herpertz: 15% in a lymphedema clinic;<sup>9</sup>
- Schmeller: 8-17% in lymphedema clinics in Germany;<sup>10</sup>
- Forner: 18.8% of lower limb edema in a Lymphedema Unit;<sup>11</sup>
- Schook: 6.5% of the children with the referral diagnosis of lymphedema actually suffer from lipedema;<sup>12</sup>
- Child: one in 72,000 in the uk.<sup>13</sup>

However, all the guidelines stress that these data are likely a significant underestimate because of misdiagnosis or failure by community physicians to refer patients.<sup>14-16</sup> Other studies by Földi *et al.* suggest that up to 15% to 17% of women being treated for lymphedema have lipedema as well.<sup>1, 9, 17</sup>

### Clinical, psychological and economical impact

Lipedema patients experience a wide range of physical problems such as lower limb heaviness, weakness, daily pain,<sup>18</sup> difficulties with walking, poor body image. Patients struggle finding well-fitting clothing and footwear. Emotional symptoms of irritability and anxiety are very common.

Research by Greene *et al.*<sup>19</sup> has identified that lower limb chronic edema, regardless of origin has significant psychological, social and physical implications for patients' quality of life.

Concerning cost on the impact of lipedema management, yet no formal health economic analyses have been done. As an example, the costs of lymphedema have been analyzed by Gutknecht *et al.*,<sup>20</sup> in 348 patients. They reported a global cost of € 5784 per patient a year.

#### Histopathology

Histological analysis of the adipose tissue in lipedema shows edema accompanied by moderate hyperplasia and depicts lack of the fibrotic elements frequently detected in lymphedema. Another article describes abnormal elastic fibers with an increased number of mastocytes. Some reports show abnormal histological findings, such as microangiopathy and a common prevalence of lymphatic microaneurysms in affected limbs. The other feature of the comparative histology analysis between lipedema and healthy individuals are the crown-like structures of CD68+ macrophages around lipedematous adipocytes and the high proportion of Ki-67 positive and especially as well CD34 positive adipocytes indicating a strong proliferation activity of adipose-derived stem cells and a simultaneous intensive cell-death.<sup>21</sup>

Liposuction-assisted tissue sampling yields significantly larger amount of adipose tissue-derived stromal vascular fraction (SVF) from lipedema compared to healthy individuals. However, there were no differences in cell viability and number. Surprisingly lipedematous SVF cells showed notably less adipogenic differentiation potential compared to those of healthy controls. Significantly higher lipedema SVF cell numbers expressing the mesenchymal stromal cell marker CD90 and the endothelial/pericytic marker CD146 were visualized.<sup>22</sup>

A recent study has described detailed histopathologic and molecular characterization of lipedema using lipid and cytokine quantification, in two anatomically matched samples of lipedema patients and controls:<sup>23</sup>

- increased epidermis thickness in lipedema patients;
- adipocyte hypertrophy with increased fibrosis in lipedema patients;
- aberrant lipid metabolism with normal circulating adipokines (IL-6, IL-18, lipocalin-2 and leptin), thus clearly differentiating lipedema from adiposity;
- pronounced macrophage infiltration in lipedema tissue.

It has been shown that Adipose-Derived Stem Cells from lipedema patients have a higher adipogenic differentiation potential compared to Adipose-Derived Stem Cells from healthy controls.<sup>24</sup>

## Pathophysiology

### Cardiovascular alterations

Established pathophysiology of lipedema is scarce, however the most common vascular features compromise blood capillary fragility, increased permeability and aneurysm-like structures of lymphatic capillaries: disturbance of lymphangiomotoric activity, impaired veno-arteriolar reflex<sup>25</sup> and macroangiopathy with increased aortic stiffness.<sup>26</sup>

The functional alterations of the lymphatic vasculature have been demonstrated in lipedema patients by abnormal lymphoscintigraphic patterns.<sup>27, 28</sup> Impaired lymphatic transport have been shown in lipedema patients in early stages. Recent studies suggest that a tortuous lymphatic pathway may be considered a typical pattern of lipedema.<sup>29</sup> More advanced lymphatic transport abnormalities are associated with severe lipedema.<sup>30</sup> This is also supported by recent finding of a new biomarker of lymphatic dysfunction, platelet factor 4, a plasma-circulating exosomal signature protein.<sup>31</sup>

In line with the previous results if lymphatic vessels in lipedema lower limbs are insufficient, the leakage of diet-

derived free fatty acids might contribute to the growth of lower limb adipose tissue. If this theory is true, the promotion of lymphatic endothelial integrity or the prevention the liberation of adipogenic factors from the lymphatics could be effective.<sup>32</sup>

Cardiovascular clinical studies demonstrated a variety of alterations that were typical for lipedema patients as compared to matched controls:

- altered two-dimensional transthoracic echocardiography parameters (increased left atrial and left ventricular dimensions, higher end-diastolic and end-systolic volumes, transmittal flow velocities);<sup>33</sup>
- significantly impaired left ventricular apical rotation and twist;<sup>34</sup>
- altered mitral annulus morphological variables (enlarged end-systolic and end-diastolic diameter, perimeter, area) and function (weaker mitral annular fractional area change);<sup>35</sup>
- greater global and mean segmental left ventricular (LV) circumferential and area strains<sup>36</sup> detected by 3D speckle tracking echocardiography.

Lower body compression with flat-knitted pantyhose led to a significant decrease in basal rotation whereas apical rotation increased nearly to the same degree leading to the persistence of LV twist at the same value.<sup>34</sup> Significantly higher end-diastolic and end-systolic volumes were measurable along with a notable increase of ejection fraction after an hour use of compression pantyhose.<sup>34</sup> The simultaneous change of basal and apical LV rotations with persistent LV twist in part gives rise to an adaptation mechanism which may involve a quasi-neutralization of fluid shift caused by compression garment along stimulating venous flow and higher cardiac preload.

### Electrolyte dysbalance

According to the latest findings, elevated skin sodium content was shown by magnetic resonance investigation.<sup>37</sup> Lymphatic dysfunctions may impair the clearance of sodium in the interstitial space, as Crescenzi *et al.*<sup>37</sup> have hypothesized to explain that adipose accumulation is associated with sodium accumulation in women with lipedema compared to matched controls.

### Neurological alterations

The affected subcutaneous regions are often tender and painful, which may cause difficulties in the application of bandaging, however, this pain is improved after decongestion<sup>38</sup> as well as liposuction.<sup>39</sup>

Schmeller *et al.*<sup>10</sup> and Wollina *et al.*<sup>39</sup> demonstrated



with tumescent local anesthesia (TLA), super-TLA, and vibrating cannulas an improvement in pressure sensitivity, edema, bruising, functional limitation, and aesthetic discomfort.

Reduced amplitude of sensory nerve action potential shown by nerve conduction could be attributed to either mechanical forces (edema and more likely increased amount of subcutaneous adipose tissue), biochemical factors, *i.e.* the inflammation of sensory nerves derived from sympathetic nerve fibers distributing among adipocytes. If microangiopathy and subsequent inappropriate peripheral nerve nourishment exists it may further aggravate innervation abnormality.<sup>25</sup>

Another interesting feature is the higher incidence of migraine among lipedema probands compared to control population.<sup>40</sup>

#### Hormonal influence

Lipedema often manifests at puberty and tends to improve after menopause. This observation together with adipose tissue enlargement localization, raises the question of sex hormonal influence of lipedema adipogenesis.

Estrogen has a direct influence on white adipose tissue through estrogen receptors (ER) (ER $\alpha$ ,  $\beta$  and G protein-coupled estrogen receptors). Considered the difference of androgenic and gynoid adiposity, this effect is likely to be body region-specific. Regardless of “hormonal age”, estrogen may directly drive both lipogenesis and lipolysis locally through modulating lipoprotein lipase activity and Lipin 1 mRNA expression. Estrogen also has a role as a

central mediator for food intake and energy expenditure in the hypothalamus. If an altered ER pattern also exists centrally (not only in the fat tissue), but this may also provide a hypothetic explanation for difficulties in weight loss in patients suffering from lipedema.<sup>25</sup>

A recent study has reported a variant in Aldo-Keto Reductase 1C1 in a family with non-syndromic lipedema, the gene encoding for an aldo-keto reductase catalyzing the reduction of progesterone to its inactive form, 20- $\alpha$ -hydroxyprogesterone.<sup>41</sup>

Hypothyroidism is obviously a common feature in lipedema. According to a recent, concise report on a single-center patient cohort nearly 1/3 of the patients are diagnosed with this type of thyroid dysfunction.<sup>42</sup>

#### Clinical manifestations of lipedema

Patients present a symmetrical and abnormal increase of adipose tissue from the hips, involving the buttocks, thighs and calves (Figure 1), always affecting bilaterally both lower limbs and sparing feet, provoking a visual effect of “Cuffing sign” (Figure 2). There is an evident disproportion in the distribution of the fat.<sup>43</sup> Patients complain that edema in lower limbs may worsen at the end of the day and is often related to the orthostasis and heat with an increased sensitivity to pain and appearance of spontaneous or minimal trauma-induced bruising. These are the most significant differences between lymphedema and lipedema.<sup>44, 45</sup> Other symptoms include plantar arch abnormalities, cold skin and spontaneous or minor trauma-induced pain.



Figure 1.—Types of lipedema.



Figure 2.—Cuffing sign.

The diagnostic criteria for lipedema were first described in 1951 by Wold *et al.*<sup>46</sup> and have been modified in recent years by Herbst (Table I).<sup>47</sup>

In a study of our group, the clinical manifestations of 112 patients with lipedema were compared to a sample of 100 patients with lower limb lymphedema, using a CART (Classification and Regression Tree) algorithm method. Four variables were identified as having a higher weight in discriminating lipedema from lymphedema. These variables could be considered as major criteria for diagnosis of lipedema: bruising, disproportion between the upper and lower body-halves, bilateral and symmetrical involvement and unaffected feet.<sup>48</sup>

The frequent association with obesity, that is the most frequent comorbidity, induces the scientific community to link all the progression of lipedema symptoms with the progression of obesity. For some authors, the association with obesity is essential; 88% of their lipedema patients are obese (Body mass index (BMI) >30 kg/m<sup>2</sup>), the li-

TABLE I.—*Diagnostic criteria for lipedema.*

Almost exclusive occurrence in women

Bilateral and symmetrical nature with minimal involvement of the feet

Minimal pitting edema

Pain, tenderness, and easy bruising

Persistent enlargement despite elevation of the extremities or weight loss

Increased vascular fragility; easy bruising



Figure 3.—Joint hypermobility in a lipedema patient.

pedema patient with normal weight is a rarity.<sup>49</sup> In our experience, obesity is linked with progression of lipedema and is the more frequent comorbidity. However, 40% of our patients are slim or normal weight, with a clear disproportion of volume between the upper and lower part of the body.

Joint hypermobility has been associated with the condition in 58% of patients with lipedema, suggesting that these may be a comorbid condition.<sup>18, 50</sup> Joint hypermobility syndrome is a connective tissue disorder characterized by joint instability, chronic pain, and minor skin changes present in approximately 3% of the general population.<sup>51</sup> In our sample of 73 patients the prevalence of hypermobility was 44% with a Beighton Score >3 (Figure 3).<sup>52</sup>

Concerning disease evolution, it is still pending whether lipedema is truly a progressive condition. In our cohort study, the change of volume at long term was stable in nearly 2/3 of the patients. Progression of lipedema, described as a change of volume superior to 10%, was related to weight increase.<sup>53</sup>

Lipedema can be classified in 5 types depending on the distribution of fat (Figure 1):<sup>3, 10, 14-16</sup>

- type I: increased deposit of fat in gluteus, hips and thighs;
- type II: lipedema extends to knees with a fat pad in the internal zone of the knees;
- type III: lipedema extends from hips to ankles;
- type IV: upper limbs are affected;
- type V: only lower part of the legs are affected.



Based on inspection and palpation, lipedema can be classified in 4 clinical stages of severity:<sup>3, 10, 14-16</sup>

- stage 1: the skin surface is normal, and the subcutaneous fatty tissue has a soft consistency but multiple small nodules can be palpated;
- stage 2: the skin surface becomes uneven and harder due to the increasing nodular structure (big nodules) of the subcutaneous fatty tissue (liposclerosis);
- stage 3: is characterized by lobular deformation of the skin surface due to increased adipose tissue. The nodules vary in size and can be distinguished from the surrounding tissue on palpation. The phenomenon of “orange peel” can be seen by pressing the skin;
- stage 4: lipolymphedema.

Imaging tests that provide structural and functional information of the lymphatic system such as indirect lymphography, lymphofluoroscopy, magnetic resonance lymphangiography and high-resolution duplex ultrasounds have failed to show any specific or pathognomonic findings of lipedema that could assist in setting a definitive diagnosis.<sup>54, 55</sup>

### Management of lipedema

In different countries lipedema is diagnosed and managed by different units including rehabilitation services, plastic surgery, angiology, vascular surgery or dermatology departments. However, a recently published guideline states that lymphedema services are the most appropriate setting for the management of patients with lipedema, due to overall expertise.<sup>16</sup>

Currently it is still very difficult to cure lipedema, and this important topic represents a great challenge for the Scientific Community and for the best practice all over the world. Therefore, honest and understandable information has to be provided to the patient.<sup>16</sup>

The main goal remains the management of the symptoms and self-care enhancement. This is essential as it is the basis of chronic diseases management. Once diagnosis is established secondary prevention is a major objective.

The goals of treatment are:<sup>15</sup> 1) to relieve symptoms; 2) to slow or stop the progression of the disease; and 3) to prevent complications.

It is essential that the patient and physician set realistic expectations and simultaneously address the psychological and emotional issues associated with lipedema.

As it has been recently stated by Cavezzi *et al.*,<sup>56</sup> translational medicine is achieving increasing acceptance within the scientific community. This has relevant repercussions on the management and new opportunities for patients

suffering lymphological diseases. Likewise, lipedema patients need not only the best-practice accepted approach but a more holistic attitude.

Lipedema management with a comprehensive approach will benefit the patients more than the basic pathophysiological management. The main active epigenetic sociobiologic factors related to lipedema as obesity, pro-inflammatory nutrition, hyperactivation of stress axis, and sedentarism must be addressed. They significantly influence chronic degenerative phlebo-lymphatic diseases.<sup>57</sup>

### Benefits of lipedema management<sup>16</sup>

Patients with lipedema who follow the recommendations and treatments prescribed in a Lymphedema Unit usually report reductions in heaviness and pain, and better shape of their lower limbs, weight control, mobility and quality of life. The care of lipedema patients also aims to prevent obesity and disease progression and to reduce the impact on musculoskeletal system and its normal function.

The main components of lipedema management, once accurately diagnosed, are multiple. Psychosocial support, including management of expectations and education, family planning, pregnancy advice and genetic counseling are essential. Dietary approach, weight management, physical activity and improving mobility must be outlined. Daily instruction is necessary for skin care, compression therapy, and pain management.<sup>16</sup>

Pharmacological treatment for edema and inflammatory effects (corticosteroids, hormones and their antagonists or modulators, diuretics, flavonoids, nutraceuticals, etc.) are under investigation so their use is not evidence-based.

The management of lipedema is highly dependent on BMI.<sup>58</sup> Weight loss has been shown to reduce symptoms despite the dogmatic belief that lipedema fat was not related to body total fat.<sup>59</sup> Basic recommendations for weight loss may be deceiving, therefore the advice must be weight control. Weight gain is one of the most important predictors of progression.<sup>53</sup>

### Information of the disorder and education in self-care

For all the patients, information of the disorder and education in self-care are essential to the long-term success in the management of lipedema. These include informing the patient that their commitment in the self-care plan will have many benefits in their quality of life. That it remains unknown if lipedema is progressive (some are diagnosed in early stages despite their advanced age, so the factors leading to lipolymphedema are unknown). Nevertheless, all efforts must avoid this possibility and all decisions be

patient centered. Achievable goals will be set as well as realistic. Long term benefits are mainly due to weight control, physical activity and adequate compression.

### Diet

Nutrition is an important component of the treatment of any disorder. Many diets have been recommended for patients with lipedema but none of them has been clearly shown the efficacy in controlling the disease.

There are two types of patients: with obesity or without obesity.

Although weight loss has failed to have any influence on lipedema volume,<sup>46, 47</sup> this is still a controversial issue. The benefits are undeniable: a better general health status; a better mobility, less joint pain when associated with osteoarthritis; and less difficulty in using compression garments.

In patients with normal BMI and lipedema, maintaining accurate weight can help the patient to avoid the progression of the disease, prevent the impairment of mobility and progress of osteoarthritis.

Regarding diets, Rare Adipose Disorders diet<sup>47, 60</sup> is under an extensive research by Dr Herbst and associates. It is based on a reduction of pasteurized dairy products, animal fats, simple sugars, carbohydrates, salt and artificial preservatives, flavors and sweeteners. Another proposed diet is Harvie and Howell diet: Mediterranean diet associated to restriction in calorie intake 2 days a week.<sup>61</sup> Mediterranean diet can be a good strategy as it has shown to reduce fat mass in lipedema patients.<sup>62</sup>

While these studies proceed appreciating the difficulty in complying with the relatively rapid change of habits, our recommendation is the Mediterranean diet with a reduction in the intake of carbohydrates, especially in the second half of the day. Anti-inflammatory diets and increasing the intervals between the meals have been suggested, although more research is needed in this field.<sup>63</sup>

### Physical activity

Whereas the definition of lipedema implies that fat legs are not reduced by diet and exercise,<sup>47</sup> the benefits of physical activity have been seen in many clinics and is a strong recommendation for the patients with lipedema independently from the severity of the disease.<sup>14, 15</sup>

Physical activity should target weight control and realistic weight loss if possible. This usually affects upper body half to a greater extent than the lower body half.<sup>15, 64</sup> It has been shown that exercises involving the leg and calf muscles increase lymphatic drainage and venous flow, thereby

reducing or preventing edema.<sup>65</sup> Benefits derived from physical activity are evident and include improvement in muscle strength, mobility (which prevents or improves joint problems), self-esteem, and general wellbeing.

Exercise in patients suffering from lipedema should be aerobic and progressive, therefore avoiding high intensity activities that could cause or aggravate pain and bruising.<sup>16</sup> Aquatic activity is highly recommended in forms of swimming or subaquatic training.<sup>16</sup> Despite the scarce research in this field, a specifically designed aquatic protocol has shown a positive impact on chronic leg swelling.<sup>66</sup> Water density, temperature, hydrostatic pressure and buoyancy can be exploited to work on effects related to gravity, resistance and joint impact, this is especially useful in obese patients. Exercises in the water can stimulate the neuromuscular and metabolic systems, with a positive psychological impact.

To assess the efficacy of compression garments and the effect of aerobic exercise in LL volume and in Percentage of Water Content (PWC) using a bioimpedance device, our group performed a pilot study in mild lipedema patients.<sup>67</sup> With only one session of aerobic-supervised-exercise plus compression, the mean of volume reduction was 313 ml, and PWC at the ankle and the leg decreased, showing the benefits of exercise plus compression in mild lipedema patients. This result requires further investigation.

### Decongestive lymphatic therapy

Decongestive Lymphatic Therapy is useful in managing lymphedema; however, it has shown only very limited efficacy in pure lipedema where the problem is excess fat accumulation rather than excess fluid or lymphatic dysfunction.<sup>8, 68</sup>

Manual lymphatic drainage can have some benefits in reducing capillary fragility in lipedema patients,<sup>69</sup> and can help manage symptoms as pain and discomfort.<sup>60</sup>

The scarce evidence in its efficacy in volume reduction and in the prevention of progression motivated some experts to discourage its routine prescription and consideration as the gold standard of treatment.<sup>54, 63</sup>

### The role of compression

The use of compression aims to reduce symptoms (pain, heaviness) and edema<sup>70</sup> and to streamline limb contours.

In case of pitting edema, decongestion with multilayer bandages is essential before prescribing medical compression garments in the maintenance phase.

As fat is not reducible by compression, the garments are meant to avoid the accumulation of fluid in order to

prevent swelling and possible progression to lymphatic insufficiency.<sup>15, 16</sup> There are currently no guidelines to prescribe compression garments for lipedema, related to the type of garment, fabric, or the level of pressure. No reported research is available concerning the type of hosiery and the level of compression. Therefore, the prescription provided by the lymphologist is empiric and experience based. In our experience, a phlebologist is more likely to prescribe round-knitted, while a lymphologist will prescribe flat-knitted garment. It is likely that lower levels of compression may be suitable for lipedema, but this approach has not been supported by our study in which patients equally tolerated class 2 and 3 round-knitted panty-hoses.<sup>71</sup>

In less advanced stages of lipedema, class 2 circular-knitted ready-to-wear garments are adequate to drain the mild edema and improve the heaviness symptoms. Immediate benefits have been reported. At this stage, since feet are spared and full pantyhose, including the feet, are not easy to tolerate, footless leggings can be a good option. They can be worn during the day, especially during summertime and during exercise, providing the feet do not swell (Figure 4). Patients report that their symptoms are alleviated from the beginning.



Figure 4.—Legging circular knitted class 2.



Figure 5.—Pantyhose flat knitted class 2.

If the patient has obesity or presents fat lobes, these stockings will not be well tolerated thus flat-knitted custom-made garments are preferred.

In more advanced stages, a class 2 circular knit full pantyhose is recommended during the day, except in cases with larger legs or deformity of the limbs that may need a flat-knitted tissue (Figure 5).

Compression in two pieces, such as capri garment combined with knee-length compression socks, can improve the doff-and-donning difficulty in older patients that need a flat-knitted tissue and have osteoarthritis of the hands (Figure 6).<sup>11</sup>

A recent survey of patients with lipedema reported that the top 3 reasons for wearing compression garments were the following: perception of being supported (73%), alleviation of lipedema pain (67%) and improved mobility (54%). Sometimes patients cannot tolerate compression garments, so their compliance is extremely low with appropriate compression in the maintenance phase.<sup>72</sup>

### Other treatments

Shock wave therapy, stimulating lipid mobilization and lipolysis has been shown to smooth the skin in lipedema patients.<sup>73</sup> Anti-inflammatory and anti-fibrotic effects and the activation of the lymphatic flow have also been suggested.





Figure 6.—Capri garment in flat-knit class 2.

Other therapeutical options have been used in lipedema: Electrostatic massage therapy (Deep Oscillation®; Physiomed, Turin, Italy); Self-lymphatic drainage or dry skin brushing,<sup>14, 16</sup> Deep breathing.<sup>74</sup> Further research is needed to demonstrate its benefits in lipedema patients.

### Surgical treatment

Lipedema is most often combined with overweight status. In general, bariatric surgery is considered in patients with BMI  $\geq 40$  kg/m<sup>2</sup> or 35-40 kg/m<sup>2</sup> with type 2 diabetes or hypertension, who have tried all appropriate non-surgical methods to achieve weight loss.<sup>16</sup> This intervention is occasionally applied in lipedema and results mostly coming from anecdotal reports are controversial;<sup>75</sup> however, a single clinical report presenting two cases showed its efficacy.<sup>76</sup>

For patients who get insufficient benefit from conservative therapy, the following two surgical options may be available: liposuction and debulking surgery.<sup>77</sup>

### Liposuction

#### Dry liposuction

Until the 1990s, interventions usually comprised the classical dry liposuction under general anesthesia which was found to damage lymphatics in patients with lipedema causing frequent postoperative edema formation.<sup>17, 78</sup> The application of sharp and thick cannulas sometimes provoked excessive bleeding.<sup>17</sup>

#### Wet liposuction

Dry liposuction was later replaced by wet liposuction<sup>79-87</sup> using liquid infiltration throughout the treatment area prior to adipose tissue aspiration to spare lymphatic vessels.<sup>79</sup> Types of wet liposuction include wet, super wet and tumescent.<sup>83</sup> Discrimination among the different methods is based on the amount of infiltrated solution. The amount of fluid injected is less than the amount of fat (1:1.5-2 ratio of infiltrate to aspirate) which will be removed in wet liposuction.

Wet liposuction regularly uses a combination of a strong vasoconstrictor and a local anesthetic dissolved in saline solution for a safer and less traumatic procedure which always exceeds the cosmetological outcome of dry liposuction.

#### Superwet liposuction

Super wet liposuction is similar to the wet technique however the amount of fluid is nearly equal with the total amount of fat (1:1) being aspirated.<sup>83</sup>

#### Tumescent liposuction

In tumescent liposuction, the amount of fluid is approximately three times higher than the amount of fat desired to be removed. The administered solution causes the operative area to become swollen with fluid thus assisting the separation of fat cells. Then microcannulas are inserted through small incisions.<sup>17, 79, 83</sup> This is done to minimize liposuction-associated complications.

Basically, two dominant methods are widely applied in tumescent liposuction: vibration-assisted<sup>39, 79-83</sup> and water-jet-assisted.<sup>84, 85</sup> The first is the most popular and vibration gives additional benefit for the minimization of tissue damage. Water-jet-assisted technique requires less volume for infiltration compared to classic tumescent method reducing the risk of local anesthesia overdose and facilitating visual control of limb shape.

#### Laser-assisted liposuction

Laser-assisted liposuction seems to be superior to other types of liposuction, providing a combination of limb con-

touring and skin tightening in younger non-obese patients. However, it has proved to work as well in a serial of older lipedema sufferers.<sup>88</sup>

### Mega-liposuction

In mega-liposuction (aspirated volume > 5000 ml) fluid and electrolyte monitoring and if needed their supplementation are of paramount importance.<sup>83, 89</sup>

### Cannula positioning

The crisscross technique, which popular in aesthetic surgery, is discouraged because of the higher risk of lymph vessel damage with potential development of secondary lymphedema.<sup>90</sup>

Instead, cannulas are advised to position parallel to lymphatic branches.<sup>17, 39, 83, 90</sup>

### Adjunctive therapy

Liposuction does not always guarantee desired success in limb reshaping therefore has to be completed with removal of excess skin, thigh lifting, laser lipolysis or even debulking.<sup>39, 88</sup>

### The role of general anesthesia

Tumescent technique is usually combined with general anesthesia. This is done in order to make the operation tolerable for the patients, especially when mega-liposuction is carried out.<sup>90</sup> This allows the number of local anesthetics to be substantially reduced.<sup>83, 85</sup> However, this combined technique may increase the rate of severe side effects (e.g. thrombosis).<sup>39, 83</sup>

### Debulking

In complicated and advanced cases of lipedema with severe mechanical limitations or limb irregularities, a more invasive surgical approach consisting of excision of large-localized deposits of fat tissue ("lumps") as a debulking procedure (lumpectomy) may be considered.<sup>91</sup> However, this technique is usually associated with the development of lymphatic insufficiency.

### The objective assessment of the outcomes of liposuction

Liposuction in lipedema compared to aesthetic lipoaspiration was found to be safer in terms of fat embolization.<sup>39</sup>

Liposuction applied in large patient cohorts appeared to be equivocally successful in terms of quality of life and volume reduction without major complications.<sup>39, 40, 79-88</sup> Schmeller *et al.*<sup>80</sup> and Wollina *et al.*<sup>39</sup> reported very low

frequency of postoperative infection and bleeding (1.4 and 0%, 0.3 and 0.3%; respectively). The longest follow-up periods belong to the long-term clinical trial of Baumgartner *et al.*<sup>84</sup> showing comparisons between baseline and 4-, 8-, 12-year follow-up periods regarding pain, edema, bruising, mobility, cosmetic impairment, quality of life. Also reported was overall impairment and the need for conservative decongestive therapy among women with lipedema having bilateral leg liposuction. Durable positive effects were recorded in all points of view regardless of the length of postoperative observational periods.<sup>84</sup> Dadras *et al.* recruited notably larger number of stage 3 lipedema patients<sup>82</sup> compared to Baumgartner *et al.*<sup>81</sup> The study demonstrated that liposuction for stage 2 lipedema provides a more sustainable improvement in quality of life and a larger decrease in the necessity for conservative therapy than liposuction treatment for stage 3 lipedema.

In particular, liposuction, especially in advanced stages of lipedema, is a time and energy-consuming intervention, therefore early recognition seems to be pivotal; thus, liposurgery could be less burdensome both for the patients and physicians. However consistent criteria to identify the ideal timing or patient characteristics for liposuction are lacking. In advanced lipedema stages, multiple sessions are frequently needed to decrease robust amounts of adipose tissue. A recent narrative review of 140 publications of surgical approaches found notable differences in treatment strategies and methodologies as well as patient cohorts and organization.<sup>83</sup> Nevertheless, there is no clear and high-grade evidence for quality standards, uniform surgical treatment guideline as well as patient selection criteria and well-established patient stratification that may prevent useless overtreatment and subjecting patients to unnecessary risks.

Liposuction, mostly performed by plastic surgeons, ameliorates self-esteem, provides improvement from the aesthetical and reconstructive points of view so it is a dual-purpose, an aesthetic and reconstructive procedure.<sup>92</sup>

Unfortunately, lipedema surgical treatments are usually not reimbursed by health insurance companies, thus representing a major burden for a successful care in appropriately selected cases.<sup>3</sup>

### Microsurgery

Microsurgery (e.g. lympho-venous or lympho-lymphatic anastomoses, lymph node transfer) has no role in pure, uncomplicated lipedema according to the current knowledge as extensive search in English and German literatures gave no evidence to confirm the eligibility.

In lipo-lymphedema (combination of lipedema with manifest lymphatic insufficiency) when the advanced stage of lymphedema remains refractory to conventional conservative therapy lymphatic microsurgery could really be a treatment option.<sup>93</sup>

Nevertheless, nomenclature seems to be incoherent in the determination of lipedema. The most advanced form of lymphedema with giant adipose tissue enlargement due to severe lymphatic congestion is occasionally labeled as secondary lipedema.<sup>94</sup> This form could truly be benefited from the application of lymphatic microsurgery however the reservation of the noun 'lipedema' is favorable just for classic lipedema without using the adjectives "primary" and "secondary."

### Lipedema curriculum

Unlike the treatment of venous diseases, lipedema, as well as lymphedema care-related curriculum and regular training, has remained undefined by any form of international consensus. However, there are a few documents<sup>95</sup> that support the need for full lipedema specialty training programs for professional lymphologists that remains unmet. The recent consensus paper on phlebological training requirements may be an optimal template to pursue the construction of lymphology curriculum encompassing lipedema. However, lymphologist specialty does not exist in most countries. The care of lipedema is mostly practiced by dermatologists and plastic surgeons. According to the subchapters of the phlebology curriculum document, lipedema specialists need to know the principles of basic and clinical science, diagnosis and disease management. They also need the skills of liposuction if the lipedema specialist performs aspiration of adipose tissue. However, the knowledge and skills of exclusive diagnostic and interventional phlebological procedures may be optional. Lipedema patients need a standard of care all around the world that is only possible with high quality training programs among professionals that are not still validated.<sup>96</sup>

### Conclusions

Lipedema is an underdiagnosed and not rare disease with an important impact in the patient's quality of life. Unfortunately, many affected persons remain misdiagnosed. To avoid the effects of misinformation lipedema must be promptly addressed. The objectives in the management are a reduction in heaviness and pain, improved shape of the affected extremities, weight control, an improvement in mobility and in the quality of life. This approach must be

integrative and multidisciplinary, looking for a change in patients' habits. The treatment includes, depending on the severity, physical therapies, compression garments, exercise, diet, psychological support, and surgical treatment in selected cases. Solving the "mystery" of the pathophysiology may bring us closer to less invasive and more widely available therapies.

### References

1. Foldi E, Foldi M. Lipedema. In: Foldi M, Foldi E, editors. *Foldi's Textbook of Lymphology*. Munich, Germany: Elsevier GmbH; 2006. p.417-27.
2. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 11th Revision; 2020 [Internet]. Available from: <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1172950828> [cited 2021, Apr 13].
3. Halk AB, Damstra RJ. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. *Phlebology* 2017;32:152-9.
4. Buso G, Depairon M, Tomson D, Raffoul W, Vettor R, Mazzolai L. Lipedema: A Call to Action! *Obesity* (Silver Spring) 2019;27:1567-76.
5. Clinical Queries del PubMed [Internet]; Bethesda (MD): National Library of Medicine (US). c1993; 2020 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.html> [cited 2021, Apr 13].
6. Web of Science. New York: Thomson Reuters; 2021 [Internet]. Available from: [https://apps.webofknowledge.com/WOS\\_GeneralSearch\\_input.do?product=WOS&SID=F5x3DtEkJaFY5SaMhkv&search\\_mode=GeneralSearch](https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&SID=F5x3DtEkJaFY5SaMhkv&search_mode=GeneralSearch) [cited 2021, Apr 13].
7. ResearchGate GmbH. Berlin. ResearchGate; 2020 [Internet]. Available from: <https://www.researchgate.net/> [cited 2021, Apr 13].
8. Fife CE, Maus EA, Carter MJ. Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. *Adv Skin Wound Care* 2010;23:81-92, quiz 93-4.
9. Herpertz U. Krankheitsspektrum des Lipödems an einer Lymphologischen Fachklinik - Erscheinungsformen, Mischbilder und Behandlungsmöglichkeiten. *Vasomed*. 1997;6:301-7.
10. Schmeller W, Meier-Vollrath I. Lipedema. In: Weissleder, Schuchhardt, editors. *Lymphedema. Diagnosis and Therapy*. Munich, Germany: Viavital Verlag GmbH; 2007. p.294-323.
11. Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review. *Clin Obes* 2012;2:86-95.
12. Schook CC, Mulliken JB, Fishman SJ, Alomari AI, Grant FD, Greene AK. Differential diagnosis of lower extremity enlargement in pediatric patients referred with a diagnosis of lymphedema. *Plast Reconstr Surg* 2011;127:1571-81.
13. Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S, *et al*. Lipedema: an inherited condition. *Am J Med Genet A* 2010;152A:970-6.
14. Lontok E, Briggs L, Donlan M, *et al*. Lipedema. A giving smarter guide. Milken Institute center for strategic philanthropy; 2017 [Internet]. Available from: <https://milkeninstitute.org/reports/giving-smarter-guide-lipedema> [cited 2021, Apr 13].
15. Dayan E, Kim JN, Smith ML *et al*. Lipedema - The disease they call FAT: An overview for clinicians. Boston, MA: Lipedema Simplified Publications; 2017.
16. Wounds UK. Best Practice Guidelines: The Management of Lipedema. London: Wounds UK; 2017.



17. Meier-Vollrath I, Schneider W, Schmeller W. Lipödem: Verbesserte Lebensqualität durch Therapiekombination. *Dtsch Arztebl* 2005;102:A1061–7.
18. Herbst KL, Mirkovskaya L, Bharhagava A, Chava Y, Te CHT. Lipedema Fat and Signs and Symptoms of Illness, Increase with Advancing Stage. *Arch Med (Oviedo)* 2015;7:1–8.
19. Greene A, Meskeel P. The impact of lower limb chronic oedema on patients' quality of life. *Int Wound J* 2017;14:561–8.
20. Gutknecht M, Herberger K, Klose K, Purwins S, Dietz D, Blome C, *et al.* Cost-of-illness of patients with lymphoedema. *J Eur Acad Dermatol Venereol* 2017;31:1930–5.
21. Suga H, Araki J, Aoi N, Kato H, Higashino T, Yoshimura K. Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. *J Cutan Pathol* 2009;36:1293–8.
22. Priglinger E, Wurzer C, Steffenhagen C, Maier J, Hofer V, Peterbauer A, *et al.* The adipose tissue-derived stromal vascular fraction cells from lipedema patients: are they different? *Cytotherapy* 2017;19:849–60.
23. Felmerer G, Stylianaki A, Hägerling R, Wang A, Ströbel P, Hollmén M, *et al.* Adipose tissue hypertrophy, an aberrant biochemical profile and distinct gene expression in lipedema. *J Surg Res* 2020;253:294–303.
24. Al-Ghadban S, Diaz ZT, Singer HJ, Mert KB, Bunnell BA. Increase in Leptin and PPAR- $\gamma$  Gene Expression in Lipedema Adipocytes Differentiated in vitro from Adipose-Derived Stem Cells. *Cells* 2020;9:430.
25. Szél E, Kemény L, Groma G, Szolnoky G. Pathophysiological dilemmas of lipedema. *Med Hypotheses* 2014;83:599–606.
26. Szolnoky G, Nemes A, Gavallér H, Forster T, Kemény L. Lipedema is associated with increased aortic stiffness. *Lymphology* 2012;45:71–9.
27. Bilancini S, Lucchi M, Tucci S, Eleuteri P. Functional lymphatic alterations in patients suffering from lipedema. *Angiology* 1995;46:333–9.
28. Forner-Cordero I, Oliván-Sasot P, Ruiz-Llorca C, Muñoz-Langa J. [Lymphoscintigraphic findings in patients with lipedema]. *Rev Esp Med Nucl Imagen Mol* 2018;37:341–8. [Spanish].
29. Tartaglione G, Visconti G, Bartoletti R, Ieria FP, Salgarello M. Rest/stress intradermal lymphoscintigraphy in diagnosis of lipedema. *World J Nucl Med* 2020;19:376–81.
30. Gould DJ, El-Sabawi B, Goel P, Badash I, Colletti P, Patel KM. Uncovering Lymphatic Transport Abnormalities in Patients with Primary Lipedema. *J Reconstr Microsurg* 2020;36:136–41.
31. Ma W, Gil HJ, Escobedo N, Benito-Martín A, Ximénez-Embún P, Muñoz J, *et al.* Platelet factor 4 is a biomarker for lymphatic-promoted disorders. *JCI Insight* 2020;5:e135109.
32. Oliver G, Kipnis J, Randolph GJ, Harvey NL. The Lymphatic Vasculature in the 21st Century: Novel Functional Roles in Homeostasis and Disease. *Cell* 2020;182:270–96.
33. Nemes A, Kormányos Á, Domsik P, Kalapos A, Kemény L, Forster T, *et al.* Left ventricular rotational mechanics differ between lipedema and lymphedema: insights from the three-dimensional speckle tracking echocardiographic MAGYAR-path study. *Lymphology* 2018;51:102–8.
34. Nemes A, Kormányos Á, Domsik P, Kalapos A, Kemény L, Szolnoky G. The impact of lower body compression garment on left ventricular rotational mechanics in patients with lipedema-Insights from the three-dimensional speckle tracking echocardiographic MAGYAR-Path Study. *Clin Obes* 2020;10:e12380.
35. Nemes A, Kovács Z, Kormányos Á, Domsik P, Kalapos A, Piros GÁ, *et al.* The mitral annulus in lipedema: insights from the three-dimensional speckle-tracking echocardiographic MAGYAR-Path Study. *Echocardiography* 2019;36:1482–91.
36. Nemes A, Kormányos Á, Domsik P, Kalapos A, Gyenes N, Kemény L, *et al.* Are increased left ventricular strains compensatory effects in lipedema? Detailed analysis from the three-dimensional speckle-tracking echocardiographic MAGYAR-Path Study. *J Clin Ultrasound* 2020;48:470–5.
37. Crescenzi R, Marton A, Donahue PM, Mahany HB, Lants SK, Wang P, *et al.* Tissue Sodium Content is Elevated in the Skin and Subcutaneous Adipose Tissue in Women with Lipedema. *Obesity (Silver Spring)* 2018;26:310–7.
38. Szolnoky G, Varga E, Varga M, Tuczai M, Dósa-Rácz E, Kemény L. Lymphedema treatment decreases pain intensity in lipedema. *Lymphology* 2011;44:178–82. [https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=22458119&dopt=Abstract](https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=22458119&dopt=Abstract)
39. Wollina U, Heinig B. Treatment of lipedema by low-volume microcannular liposuction in tumescence anesthesia: results in 111 patients. *Dermatol Ther (Heidelb)* 2019;32:e12820.
40. Bauer AT, von Lukowicz D, Lossagk K, Aitzetmueller M, Moog P, Cerny M, *et al.* New Insights on Lipedema: The Enigmatic Disease of the Peripheral Fat. *Plast Reconstr Surg* 2019;144:1475–84.
41. Michelini S, Chiurazzi P, Marino V, Dell'Orco D, Manara E, Baglivo M, *et al.* Aldo-Keto Reductase 1C1 (AKR1C1) as the First Mutated Gene in a Family with Nonsyndromic Primary Lipedema. *Int J Mol Sci* 2020;21:6264.
42. Ghods M, Georgiou I, Schmidt J, Kruppa P. Disease progression and comorbidities in lipedema patients: A 10-year retrospective analysis. *Dermatol Ther (Heidelb)* 2020;33:e14534.
43. Van Geest AJ, Esten SC, Cambier JP, *et al.* Lymphatic disturbances in lipedema. *Phlebologie* 2003;32:138–42.
44. Fries R. Ursachen suchte bei generalisierten und lokalisierten odemen. *MMW Fortschr Med* 2004;146:39–41.
45. Herpertz U. Der missbrauch des lipödems. *Lymphol Forsch Prax* 2003;7:90–3.
46. Wold LE, Hines EA Jr, Allen EV. Lipedema of the legs; a syndrome characterized by fat legs and edema. *Ann Intern Med* 1951;34:1243–50.
47. Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. *Acta Pharmacol Sin* 2012;33:155–72.
48. Forner-Cordero I, Muñoz-Langa J, Pérez-Pomares M, Ponce-Garrido AB. Clinical algorithm for differential diagnosis between lipedema and lymphedema: a CART (Classification And Regression Tree) algorithm. Proceedings of Abstracts of the 44th ESL Congress; 2018 Sep 21–22; Prague, Czech Republic. Prague: ESL; 2018.
49. Bertsch T, Erbacher G. Lipodema - myths and facts Part 1. *Phlebologie* 2018;47:84–92.
50. Beltran K, Herbst KL. Differentiating lipedema and Dercum's disease. *Int J Obes* 2017;41:240–5.
51. Kumar B, Lenert P. Joint hypermobility syndrome: recognizing a commonly overlooked cause of chronic pain. *Am J Med* 2017;130:640–7.
52. Forner-Cordero I, Muñoz-Langa J, Vázquez-Díez J. Lipedema patients have a high prevalence of joint hypermobility. Proceedings of the ISL XXVII WORLD CONGRESS 2019; 2019 Sep 23–28; Buenos Aires, Argentina. Buenos Aires: International Society of Lymphology; 2019.
53. Forner-Cordero I, Muñoz-Langa J. Is lipedema a progressive disease? A long-term follow-up in patients with lipedema. Proceedings of the ISL XXVII WORLD CONGRESS 2019; 2019 Sep 23–28; Buenos Aires, Argentina. Buenos Aires: International Society of Lymphology; 2019.
54. Kruppa P, Georgiou I, Biermann N, Prantl L, Klein-Weigel P, Ghods M. Lipedema-Pathogenesis, Diagnosis, and Treatment Options. *Dtsch Arztebl Int* 2020;117:396–403.
55. Hirsch T, Schleinitz J, Marshall M, Faerber G. Can high-resolution ultrasound be used for the differential diagnosis of lipodema? *Phlebologie* 2018;47:182–7.
56. Cavezzi A, Colucci R, Paccasassi S, Piergentili M. Lymphology and translational medicine. *Int Angiol* 2020;39:422–32.
57. Cavezzi A. Medicine and Phlebology: time to Change? *J Clin Med* 2020;9:4091.
58. Warren Peled A, Kappos EA. Lipedema: diagnostic and management challenges. *Int J Womens Health* 2016;8:389–95.
59. Bertsch T, Erbacher G. Lipodema - myths and facts Part 3. *Phlebologie* 2018;47:188–97.
60. Todd M. Diagnosis and management of lipodema in the community. *Br J Community Nurs* 2016;21:S6–12.

61. Harvie M, Howell T. The 2-day diet: the quick and easy edition. London, UK: Vermillion; 2014.
62. Di Renzo L, Cinelli G, Romano L, Zomparelli S, Lou De Santis G, Nocerino P, *et al.* Potential Effects of a Modified Mediterranean Diet on Body Composition in Lipoedema. *Nutrients* 2021;13:358.
63. Bertsch T, Erbacher G, Corda D, *et al.* Lipoedema - myths and facts Part 5. *Phlebologie* 2020;49:31–49.
64. Shin BW, Sim YJ, Jeong HJ, Kim GC. Lipedema, a rare disease. *Ann Rehabil Med* 2011;35:922–7.
65. Okhovat JP, Alavi A. Lipedema: A Review of the Literature. *Int J Low Extrem Wounds* 2015;14:262–7.
66. Giancesini S, Tessari M, Bacciglieri P, Malagoni AM, Menegatti E, Occhionorelli S, *et al.* A specifically designed aquatic exercise protocol to reduce chronic lower limb edema. *Phlebology* 2017;32:594–600.
67. - Forner-Cordero I, Tortosa-Soriano G, Alabajos-Cea A, Ponce-Garrido AB, Muñoz-Langa J. Effect of compression alone or combined with exercise in patients with lipedema. A pilot study. In: Abstracts of the 42nd European Society of Lymphology Congress. *Eur J Lymphol Relat Probl* 2016; 28: 70.
68. Szolnoky G, Borsos B, Bársony K, Balogh M, Kemény L. Complete decongestive physiotherapy with and without pneumatic compression for treatment of lipedema: a pilot study. *Lymphology* 2008;41:40–4.
69. Szolnoky G, Nagy N, Kovács RK, Dósa-Rácz E, Szabó A, Bársony K, *et al.* Complex decongestive physiotherapy decreases capillary fragility in lipedema. *Lymphology* 2008;41:161–6.
70. Reich-Schupke S, Schmeller W, Brauer WJ, Cornely ME, Faerber G, Ludwig M, *et al.* S1 guidelines: lipedema. *J Dtsch Dermatol Ges* 2017;15:758–67.
71. Flour M, Clark M, Partsch H, Mosti G, Uhl JF, Chauveau M, *et al.* Dogmas and controversies in compression therapy: report of an International Compression Club (ICC) meeting, Brussels, May 2011. *Int Wound J* 2013;10:516–26.
72. Paling I, Macintyre L. Survey of lipoedema symptoms and experience with compression garments. *Br J Community Nurs* 2020;25:S17–22.
73. Siems W, Grune T, Voss P, Brenke R. Anti-fibrosclerotic effects of shock wave therapy in lipedema and cellulite. *Biofactors* 2005;24:275–82.
74. Fetzer A, Wise C. Living with lipoedema: reviewing different self-management techniques. *Br J Community Nurs* 2015;S14:S16–9.
75. Bast JH, Ahmed L, Engdahl R. Lipedema in patients after bariatric surgery. *Surg Obes Relat Dis* 2016;12:1131–2.
76. Pouwels S, Huisman S, Smelt HJ, Said M, Smulders JF. Lipoedema in patients after bariatric surgery: report of two cases and review of literature. *Clin Obes* 2018;8:147–50.
77. Warren AG, Janz BA, Borud LJ, Slavin SA. Evaluation and management of the fat leg syndrome. *Plast Reconstr Surg* 2007;119:9e–15e.
78. Hoffmann JN, Fertmann JP, Baumeister RG, Putz R, Frick A. Tumescence and dry liposuction of lower extremities: differences in lymph vessel injury. *Plast Reconstr Surg* 2004;113:718–24, discussion 725–6.
79. van de Pas CB, Boonen RS, Stevens S, Willemsen S, Valkema R, Neumann M. Does tumescent liposuction damage the lymph vessels in lipoedema patients? *Phlebology* 2020;35:231–6.
80. Schmeller W, Hueppe M, Meier-Vollrath I. Tumescence liposuction in lipoedema yields good long-term results. *Br J Dermatol* 2012;166:161–8.
81. Baumgartner A, Hueppe M, Schmeller W. Long-term benefit of liposuction in patients with lipoedema: a follow-up study after an average of 4 and 8 years. *Br J Dermatol* 2016;174:1061–7.
82. Dadras M, Mallinger PJ, Corterier CC, Theodosiadi S, Ghods M. Liposuction in the Treatment of Lipedema: A Longitudinal Study. *Arch Plast Surg* 2017;44:324–31.
83. Ghods M, Kruppa P. Operative Behandlung des Lipödems [Surgical treatment of lipoedema]. *Handchir Mikrochir Plast Chir* 2018;50:400–11.
84. Baumgartner A, Hueppe M, Meier-Vollrath I, Schmeller W. Improvements in patients with lipedema 4, 8 and 12 years after liposuction. *Phlebology* 2021;36:152–9.
85. Sandhofer M, Hanke CW, Habbema L, Podda M, Rapprich S, Schmeller W, *et al.* Prevention of progression of lipedema with liposuction using tumescent local anesthesia: results of an international consensus conference. *Dermatol Surg* 2020;46:220–8.
86. Stutz JJ, Kralh D. Water jet-assisted liposuction for patients with lipoedema: histologic and immunohistologic analysis of the aspirates of 30 lipoedema patients. *Aesthetic Plast Surg* 2009;33:153–62.
87. Witte T, Dadras M, Heck FC, Heck M, Habermalz B, Welss S, *et al.* Water-jet-assisted liposuction for the treatment of lipedema: standardized treatment protocol and results of 63 patients. *J Plast Reconstr Aesthet Surg* 2020;73:1637–44.
88. Wollina U, Heinig B, Nowak A. Treatment of elderly patients with advanced lipedema: a combination of laser-assisted liposuction, medial thigh lift, and lower partial abdominoplasty. *Clin Cosmet Investig Dermatol* 2014;7:35–42.
89. Sandhofer M, Hofer V, Sandhofer M, Sonani M, Moosbauer W, Barsch M. High Volume Liposuction in Tumescence Anesthesia in Lipedema Patients: A Retrospective Analysis. *J Drugs Dermatol* 2021;20:326–34.
90. Wiedner M, Aghajanzadeh D, Richter DF. Differential diagnoses and treatment of lipedema. *Plast Aesthet Res* 2020;7:10.
91. Wollina U, Heinig B, Schönlebe J, Nowak A. Debulking surgery for elephantiasis nostras with large ectatic podoplanin-negative lymphatic vessels in patients with lipo-lymphedema. *Eplasty* 2014;14:e11.
92. Georgiou I, Kruppa P, Schmidt J, Ghods M. Liposuction for Lipedema: Functional Therapy or Aesthetic Procedure? *Aesthetic Plast Surg* 2021;45:212–3.
93. Spörlein A, Will PA, Kilian K, Gazyakan E, Sacks JM, Kneser U, *et al.* Lymphatic Tissue Engineering: A Further Step for Successful Lymphedema Treatment. *J Reconstr Microsurg* 2021. [Epub ahead of print]
94. Gould DJ, Mehrara BJ, Neligan P, Cheng MH, Patel KM. Lymph node transplantation for the treatment of lymphedema. *J Surg Oncol* 2018;118:736–42.
95. - British Lymphology Society. Professional roles in the care of lymphedema; 2016 [Internet]. Available from: <https://www.thebls.com/public/uploads/documents/document-54261534789017.pdf> [cited 2021, Apr 13].
96. Guex JJ, Mariani F, Maleti O, Hamel-Desnos C, Vasdekis S, Staelens I, *et al.* European training requirements in phlebology. *Int Angiol* 2019;38:345–64.

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