Morphology of Lipedema

Subjects: Cell Biology

Contributor: Ankita Poojari , Kapil Dev , Atefeh Rabiee

Lipedema is an adipofascial disorder that almost exclusively affects women. Lipedema leads to chronic pain, swelling, and other discomforts due to the bilateral and asymmetrical expansion of subcutaneous adipose tissue. Although various distinctive morphological characteristics, such as the hyperproliferation of fat cells, fibrosis, and inflammation, have been characterized in the progression of lipedema, the mechanisms underlying these changes have not yet been fully investigated. In addition, it is challenging to reduce the excessive fat in lipedema patients using conventional weight-loss techniques, such as lifestyle (diet and exercise) changes, bariatric surgery, and pharmacological interventions. Therefore, lipedema patients also go through additional psychosocial distress in the absence of permanent treatment. Research to understand the pathology of lipedema is still in its infancy, but promising markers derived from exosome, cytokine, lipidomic, and metabolomic profiling studies suggest a condition distinct from obesity and lymphedema. Although genetics seems to be a substantial cause of lipedema, due to the small number of patients involved in such studies, the extrapolation of data at a broader scale is challenging. With the current lack of etiology-guided treatments for lipedema, the discovery of new promising biomarkers could provide potential solutions to combat this complex disease.

lipedema chronic disease adipose tissue fat disorder

1. Introduction

In the clinic, lipedema is frequently misdiagnosed as obesity, lymphedema, lipodystrophies, or other fat disorders. It is distinct in its manifestation as solely affecting the upper and lower extremities with a disproportional deposition of subcutaneous fat, sparing the hands and feet [1][2]. Although the diagnosis of lipedema does not exclude the presence of obesity and lymphedema (especially the latter, which is typically present as a comorbidity in the advanced stages of lipedema), it is essential to have a correct diagnosis to manage the symptoms in the early stages of the disease [1][3]. Lipedema patients at an advanced stage experience severe long-term pain and significant psychosocial distress, including depression, eating disorders, and social isolation [4] due to fat-shaming and a lack of adequate medical treatment. Lipedema affects nearly 11% of adult women and postpubertal females globally. As it has been estimated in reports, it could potentially affect millions of adult women in the United States alone, with an incidence of approximately one in nine women [5][6]. Lipedema is characterized by tenderness to palpation, easy bruising, and the bilateral and asymmetrical expansion of inflamed subcutaneous adipose tissue (SAT) [7][8]. The manifestation of lipedema often coincides with periods of hormonal changes that occur throughout puberty, after pregnancy, or during the menopause stage [9] and may be inherited [10]. Although several morphological characteristics are altered in the SAT of lipedema patients, the mechanisms underlying such changes have not yet been clarified. In addition to the nature of the fat, the potential roles of several other factors,

such as the immune and lymphatic systems, in the development of lipedema have also been investigated. Unlike obesity, adipocyte hypertrophy and the localized deposition of fat in the SAT of lipedema patients often do not respond to dietary (caloric) restrictions, exercise, and bariatric surgery [4][11][12]. Therefore, further studies to investigate novel biomarkers and mechanistically understand lipedema's onset and progression are essential. This effort is expected to aid in the timely diagnosis and, eventually, develop treatment modalities toward a better therapeutic outcome for patients with lipedema.

2. Components of Adipose Tissue and Its Heterogeneity

The health status and function of adipose tissue (AT) depend on the fat-storing adipocytes and the complex intercellular communication between the several cell types residing within the tissue. Heterogenous AT is not solely composed of mature adipocytes but is also composed of adipocyte precursors/stem cells, immune cells, blood cells, and lymphatic capillaries consisting of endothelial cells (ECs) [13][14]. It has become evident that the growth, expansion, and physiological function of white adipose tissue (WAT), a weight-regulated organ, is highly controlled by cross-talk between each of its cellular components, with a central role for the vascular endothelium lining the blood vessels [15]. Microvessels or capillaries within the adipose vasculature are composed of a thin layer of ECs, within which pericytes—a type of supporting cell—are enmeshed, allowing for the efficient delivery of gases, fluids, and essential macromolecules to the parenchyma cells [16]. AT features continuous capillaries with tightly arranged ECs, which are impervious to paracellular leakage and oversee the delivery of nutrients in a trans-endothelial manner (i.e., through the endothelium) through highly controlled mechanisms [17][18]. This continuous endothelial arrangement is accomplished by establishing tight junctions between neighboring cells and a constant membrane along the vessels [15]. It is shown that when an individual AT achieves its maximum growth rate, it loses the ability to store lipids further, resulting in lipid leakage from the tissue, ectopic lipid deposition in peripheral organs, and a systemic deterioration in metabolic health [19]. Although the endothelium was initially thought to be merely a barrier, it has recently emerged as a dynamic unit that regulates many critical functions of AT [15], such as the volume and type of lipids stored in various fat depots [20]. To maintain a healthy microenvironment within the AT, adipocytes are surrounded by interstitial fluid (IF) and are supported by a network of extracellular matrix (ECM) proteins that provide structural integrity [21]. However, as explained above, morphologically, the SAT in lipedema is pathologically altered. Studies on lipedema have included precursor cells and mature adipocytes, as well as impaired adipose vasculature, including the adipose endothelium, the involvement of the IF and lymphatic system, ECM remodeling, and the deposition of collagen, all synchronously promoting fibrosis and edema in the affected tissue [1].

3. Morphology of Lipedema SAT

A study focused on the morphological assessment of lipedema stem cells derived from the subcutaneous flank. Lateral thigh adipose tissues (tATs) revealed a significant increase in cell number [12]. The increased cell number was accompanied by an elongated, partly spindle-shaped appearance, with rounded nuclei at 11–14 days of culture without adipogenic stimuli. However, on days 7 and 14 of culture with adipogenic stimuli, the cell morphology changed from having a spindle-like appearance to having an adipocyte-like shape [12]. Investigation of

the SAT in lipedema patients from the lower extremities showed hypertrophic and hyperplastic adipocytes, increased intercellular fibrosis [7][22], crown-like structures, elevated macrophage levels [7][23], and a morphologically distinct appearance compared to healthy control tissue [22] (**Figure 1**). It has also been reported that the AT of an individual with lipedema undergoes major structural and functional reprogramming [22], including increased unstimulated lipid release [24], tissue inflammation, and excessive fluid accumulation [6][25].

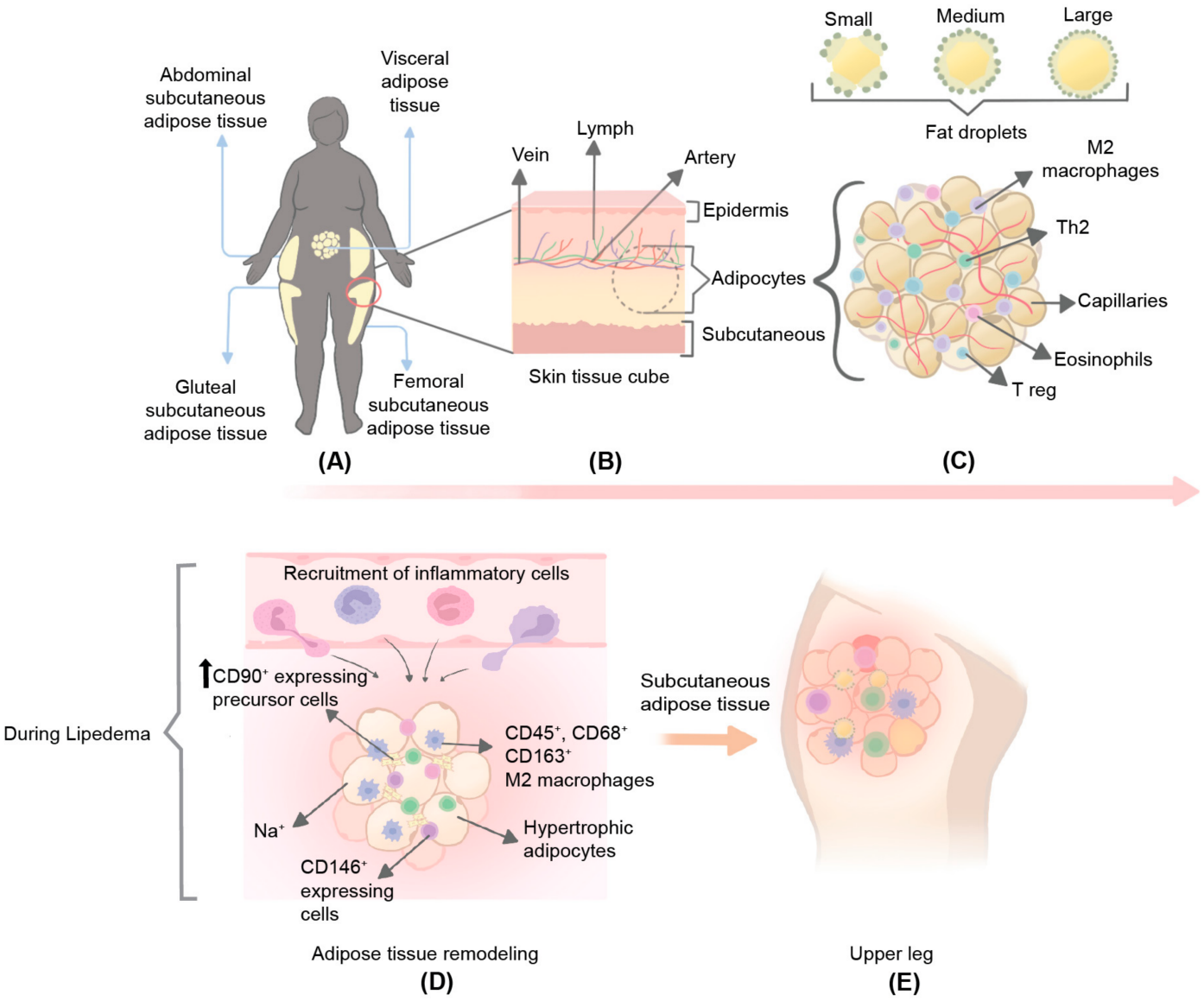

Figure 1. Representation of subcutaneous adipose tissue (SAT) characteristics pattern in lipedema. (**A**) The SAT location and deposition in the body; (**B**) skin tissue cube presenting their residing components; (**C**) characteristics of lean adipose tissue accompanied by ECM, immune cells, and various forms of typical fat droplets; (**D**) hypertrophy and hyperplasia in SAT with immune-cell requirements; and (**E**) inflammation, excessive fluid deposition, and swelling in the upper leg/thigh, which are the common characteristic of individuals with lipedema.

4. Excess Interstitial Fluid, Contributing Factors, and Consequences

The swelling caused by adipose hypertrophy occurs in a distinctively symmetrical form in lipedema, which, unlike lymphedema, does not show overt interstitial edema [26]. However, excessive fluid accumulation in the interstitial space is often a common characteristic of progressed lipedema. Increased limb capillary pressure, changes in tissue structure, extra blood vessels with excessive permeability, increased lymphatic area, and inadequate lymphatic outflow are the potential contributing factors that facilitate fluid accretion in lipedema [27].

The increased IF in lipedema allows for the palpation of individual fat lobules as nodules [7]. Moreover, the blood and lymphatic flow have been revealed to be slower in the gynoid SAT in lipedema [28]. Under inadequate flow, inflammatory and fibrotic lesions develop in SAT, leading to chronic pain and palpation [29]. Meanwhile, livedo reticularis and capillary fragility in lipedema LCT can make individuals more prone to bruising [6][30]. In nonlipedema SAT, groups of adipocytes called fat lobules readily glide over one another beneath the skin on tiny wet fibers, giving the skin a uniformly smooth and soft feel [31].

On the other hand, the lipedema tissue exhibits some defining features, such as (1) inflammation that leads to tissue fibrosis in the ECM [23][32] and (2) the formation of palpable fibrotic nodule-like structures within the skin [6]. The aberrant elastic fibers seen in the skin lesions of lipedema patients are thought to be partly caused by progressive mineralization [33]. The loss of smooth consistency and the development of pearl-sized (5 mm) nodules close to the lymph nodes are features of lipedema SAT, which represent tenderness to palpation [1][24]. Ibarra et al. examined nodules that were either within one centimeter of the skin or directly beneath it. These nodules were found to be similar to the palpable lumps felt on examination. Thus, they revealed a connection between blood vessels and hyperechoic masses (~1 cm in size) in lipedema and Dercum's disease [25]. Notably, such a mass was suggested to indicate a leaky vessel, a bruise, or inflammation around a vessel—all symptoms found in lipedema.

5. Stages of Lipedema

Lipedema involves fluid in the fat at more advanced stages of the disease. Enlarged blood vessels, skin microangiopathy, and various forms of nodules (i.e., rice-grain, pearl-sized, or larger-sized nodules in LCT) are observed during the progression of lipedema, especially in women [6][34][35][36]. Based on the tissue structure, mobilizing pattern, and pathology, lipedema is characterized by four progressive stages (**Table 1**). In stage I, the patients present with a smooth skin texture, an enlarged subdermis, pearl-sized nodules in a hypertrophic SAT layer (which are painful once in a while), and a subdermal pebble-like feel due to underlying LCT fibrosis. The following occurs in stage II: skin depressions with pearl- to apple-sized masses that form in the skin, AT, palpable nodules, and bands of perilobular fascia that thicken and contract, an inflamed appearance of the skin (due to progressive fibrotic changes), and pulling down of the skin in a mattress pattern (due to excess tissue). In stage III, patients feature more painful, increased lipedema tissue that is more fibrotic in texture with numerous large subdermal nodules and overhanding lobules of tissue, as well as fat on the arms, hips, thighs, and around the knees. Moreover, in comparison to stage I or stage II, the skin thins and loses elasticity, allowing the SAT to grow excessively and fold over, further inhibiting the flow [37], which can eventually lead to lipolymphedema or lymphedema in stage III [38]. In *stage* IV, lipedema is characterized by lipolymphedema (concomitant lymphedema) which develops in the presence of both lipedema and lymphedema, featuring large overhangs of fat tissue on the

legs or arms, and large fat tissue extrusions on the legs that progress to lipolymphedema, thus representing a more advanced stage in most cases [2]. Notably, during all stages of lipedema, lipolymphedema (a condition similar to lymphedema) can occur [39]. For this reason, lipedema is often confused with other metabolic disorders, such as lymphedema, obesity, lipodystrophies, and other fat-related diseases [10]. Therefore, investigating the dysfunctional physiological mechanisms underpinning lipedema is quite challenging for researchers.

Table 1. Stages of lipedema are categorized based on adipose tissue structure, mobilization pattern, and pathological conditions observed under clinical investigation of patients with lipedema.

Stage I	Stage II	Stage III	Stage IV
• Smooth skin texture, enlarged subdermis, and pearl-sized nodules in a hypertrophic SAT layer. • Once in a while painful and has a subdermal pebble-like feel due to underlying loose connective tissue fibrosis.	• Skin depressions with pearl-to-apple large-sized masses that form in the skin and adipose tissue. • Palpable nodules and bands of perilobular fascia thicken and contract. • Inflamed appearance of skin due to progressed fibrotic changes, pulling the skin down in the mattress pattern due to excess tissue.	• Patients feature more painful, increased lipedema tissue that is more fibrotic in texture, with numerous large subdermal nodules. • Skin thins and loses elasticity, allowing SAT to grow excessively and fold over, inhibiting flow.	• It is characterized by lipolymphedema (concomitant lymphedema with lipedema). • Features large overhangs of fat tissue on legs or arms and large fat tissue extrusion on the legs.

References

1. La Torre, Y.S.-D.; Wadeea, R.; Rosas, V.; Herbst, K.L. Lipedema: Friend and Foe. Horm. Mol. Biol. Clin. Investig. 2018, 33, 1.
2. Buso, G.; Depairon, M.; Tomson, D.; Raffoul, W.; Vettor, R.; Mazzolai, L. Lipedema: A Call to Action! Obesity 2019, 27, 1567.
3. Shavit, E.; Wollina, U.; Alavi, A. Lipoedema Is Not Lymphoedema: A Review of Current Literature. Int. Wound J. 2018, 15, 921–928.
4. Herbst, K.L. Rare Adipose Disorders (RADs) Masquerading as Obesity. Acta Pharmacol. Sin. 2012, 33, 155–172.

5. Buck, D.W.; Herbst, K.L. Lipedema: A Relatively Common Disease with Extremely Common Misconceptions. Plast. Reconstr. Surg. Glob. Open 2016, 4, e1043.
6. Herbst, K.L.; Kahn, L.A.; Iker, E.; Ehrlich, C.; Wright, T.; McHutchison, L.; Schwartz, J.; Sleigh, M.; Donahue, P.M.C.; Lisson, K.H.; et al. Standard of Care for Lipedema in the United States. Phlebology 2021, 36, 779–796.
7. 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, 1293–1298.
8. Crescenzi, R.; Marton, A.; Donahue, P.M.C.; Mahany, H.B.; Lants, S.K.; Wang, P.; Beckman, J.A.; Donahue, M.J.; Titze, J. Tissue Sodium Content Is Elevated in the Skin and Subcutaneous Adipose Tissue in Women with Lipedema. Obesity 2018, 26, 310–317.
9. 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.
10. Child, A.H.; Gordon, K.D.; Sharpe, P.; Brice, G.; Ostergaard, P.; Jeffery, S.; Mortimer, P.S. Lipedema: An Inherited Condition. Am. J. Med. Genet. Part A 2010, 152, 970–976.
11. Reich-Schupke, S.; Schmeller, W.; Brauer, W.J.; Cornely, M.E.; Faerber, G.; Ludwig, M.; Lulay, G.; Miller, A.; Rapprich, S.; Richter, D.F.; et al. S1 Guidelines: Lipedema. JDDG J. Dtsch. Dermatol. Ges. 2017, 15, 758–767.
12. Bauer, A.T.; Von Lukowicz, D.; Lossagk, K.; Hopfner, U.; Kirsch, M.; Moog, P.; Bauer, H.; Machens, H.G.; Schmauss, D. Adipose Stem Cells from Lipedema and Control Adipose Tissue Respond Differently to Adipogenic Stimulation In Vitro. Plast. Reconstr. Surg. 2019, 144, 623–632.
13. Lee, M.J.; Wu, Y.; Fried, S.K. Adipose Tissue Heterogeneity: Implication of Depot Differences in Adipose Tissue for Obesity Complications. Mol. Asp. Med. 2013, 34, 1–11.
14. Jeffery, E.; Wing, A.; Holtrup, B.; Sebo, Z.; Kaplan, J.L.; Saavedra-Peña, R.; Church, C.D.; Colman, L.; Berry, R.; Rodeheffer, M.S. The Adipose Tissue Microenvironment Regulates Depot-Specific Adipogenesis in Obesity. Cell Metab. 2016, 24, 142–150.
15. Ioannidou, A.; Fisher, R.M.; Hagberg, C.E. The Multifaceted Roles of the Adipose Tissue Vasculature. Obes. Rev. 2022, 23, e13403.
16. Van Dijk, C.G.M.; Nieuweboer, F.E.; Pei, J.Y.; Xu, Y.J.; Burgisser, P.; Van Mulligen, E.; El Azzouzi, H.; Duncker, D.J.; Verhaar, M.C.; Cheng, C. The Complex Mural Cell: Pericyte Function in Health and Disease. Int. J. Cardiol. 2015, 190, 75–89.

17. Krüger-Genge, A.; Blocki, A.; Franke, R.P.; Jung, F. Vascular Endothelial Cell Biology: An Update. Int. J. Mol. Sci. 2019, 20, 4411.
18. Hasan, S.S.; Fischer, A. The Endothelium: An Active Regulator of Lipid and Glucose Homeostasis. Trends Cell Biol. 2021, 31, 37–49.
19. Hammarstedt, A.; Gogg, S.; Hedjazifar, S.; Nerstedt, A.; Smith, U. Impaired Adipogenesis and Dysfunctional Adipose Tissue in Human Hypertrophic Obesity. Physiol. Rev. 2018, 98, 1911–1941.
20. Yucel, N.; Arany, Z. Fat, Obesity, and the Endothelium. Curr. Opin. Physiol. 2019, 12, 44–50.
21. Rutkowski, J.M.; Davis, K.E.; Scherer, P.E. Mechanisms of Obesity and Related Pathologies: The Macro- and Microcirculation of Adipose Tissue. FEBS J. 2009, 276, 5738–5746.
22. Felmerer, G.; Stylianaki, A.; Hägerling, R.; Wang, A.; Ströbel, P.; Hollmén, M.; Lindenblatt, N.; Gousopoulos, E. Adipose Tissue Hypertrophy, an Aberrant Biochemical Profile and Distinct Gene Expression in Lipedema. J. Surg. Res. 2020, 253, 294–303.
23. Al-Ghadban, S.; Cromer, W.; Allen, M.; Ussery, C.; Badowski, M.; Harris, D.; Herbst, K.L. Dilated Blood and Lymphatic Microvessels, Angiogenesis, Increased Macrophages, and Adipocyte Hypertrophy in Lipedema Thigh Skin and Fat Tissue. J. Obes. 2019, 2019, 8747461.
24. Ishaq, M.; Bandara, N.; Morgan, S.; Nowell, C.; Mehdi, A.M.; Lyu, R.; McCarthy, D.; Anderson, D.; Creek, D.J.; Achen, M.G.; et al. Key Signaling Networks Are Dysregulated in Patients with the Adipose Tissue Disorder, Lipedema. Int. J. Obes. 2022, 46, 502–514.
25. Ibarra, M.; Eekema, A.; Ussery, C.; Neuhardt, D.; Garby, K.; Herbst, K.L. Subcutaneous Adipose Tissue Therapy Reduces Fat by Dual X-ray Absorptiometry Scan and Improves Tissue Structure by Ultrasound in Women with Lipoedema and Dercum Disease. Clin. Obes. 2018, 8, 398–406.
26. Shin, B.W.; Sim, Y.-J.; Jeong, H.J.; Kim, G.C. Lipedema, a Rare Disease. Ann. Rehabil. Med. 2011, 35, 922–927.
27. Allen, M.; Schwartz, M.; Herbst, K.L. Interstitial Fluid in Lipedema and Control Skin. Women's Health Rep. 2020, 1, 480–487.
28. L'Hermitte, F.; Behar, A.; Pariès, J.; Cohen-Boulakia, F.; Attali, J.R.; Valensi, P. Impairment of Lymphatic Function in Women with Gynoid Adiposity and Swelling Syndrome. Metabolism 2003, 52, 805–809.
29. Shah, J.P.; Danoff, J.V.; Desai, M.J.; Parikh, S.; Nakamura, L.Y.; Phillips, T.M.; Gerber, L. Biochemicals Associated with Pain and Inflammation Are Elevated in Sites Near to and Remote from Active Myofascial Trigger Points. Arch. Phys. Med. Rehabil. 2008, 89, 16–23.
30. Szolnoky, G.; Nagy, N.; Kovács, R.K.; Dósa-Rácz, É.; Szabó, A.; Bársony, K.; Balogh, M.; Kemény, L. Complex Decongestive Physiotherapy Decreases Capillary Fragility in Lipedema.

Lymphology 2008, 41, 161–166.

31. Guimberteau, J.C. Approche Endoscopique des Aponévroses. Continuité Fibrillaire dans les Fascia et Aponévroses. Ann. Chir. Plast. Esthétique 2012, 57, 465–466.
32. Felmerer, G.; Stylianaki, A.; Hollmén, M.; Ströbel, P.; Stepniewski, A.; Wang, A.; Frueh, F.S.; Kim, B.S.; Giovanoli, P.; Lindenblatt, N.; et al. Increased Levels of VEGF-C and Macrophage Infiltration in Lipedema Patients without Changes in Lymphatic Vascular Morphology. Sci. Rep. 2020, 10, 10947.
33. Paolacci, S.; Precone, V.; Acquaviva, F.; Chiurazzi, P.; Fulcheri, E.; Pinelli, M.; Buffelli, F.; Michelini, S.; Herbst, K.L.; Unfer, V.; et al. Genetics of Lipedema: New Perspectives on Genetic Research and Molecular Diagnoses. Eur. Rev. Med. Pharmacol. Sci. 2019, 23, 5581–5594.
34. Eklof, B.; Perrin, M.; Delis, K.T.; Rutherford, R.B.; Gloviczki, P. Updated Terminology of Chronic Venous Disorders: The VEIN-TERM Transatlantic Interdisciplinary Consensus Document. J. Vasc. Surg. 2009, 49, 498–501.
35. Wiedner, M.; Aghajanzadeh, D.; Richter, D.F. Differential Diagnoses and Treatment of Lipedema. Plast. Aesthetic Res. 2020, 7, 10.
36. Al-Ghadban, S.; Pursell, I.A.; Diaz, Z.T.; Herbst, K.L.; Bunnell, B.A. 3D Spheroids Derived from Human Lipedema Ascs Demonstrated Similar Adipogenic Differentiation Potential and Ecm Remodeling to Non-Lipedema Ascs In Vitro. Int. J. Mol. Sci. 2020, 21, 8350.
37. Fife, C.E.; Maus, E.A.; Carter, M.J. Lipedema: A Frequently Misdiagnosed and Misunderstood Fatty Deposition Syndrome. Adv. Ski. Wound Care 2010, 23, 81–92.
38. Herbst, K.L.; Mirkovskaya, L.; Bharhagava, A.; Chava, Y.; Te, C. Lipedema Fat and Signs and Symptoms of Illness, Increase with Advancing Stage. Arch. Med. 2015, 7, 1–8.
39. Rasmussen, J.C.; Aldrich, M.B.; Fife, C.E.; Herbst, K.L.; Sevick-Muraca, E.M. Lymphatic Function and Anatomy in Early Stages of Lipedema. Obesity 2022, 30, 1391–1400.