

EVIDENCE BASED STATEMENT

DOMAIN **10**, Statement **1**

TOPIC: “LYMPHEDEMA & LIPEDEMA PATHO-PHYSIOLOGY”

SEARCH TERMS & SOURCES

((lymphedema[MeSH Terms]) AND ((pathophysiology[MeSH Terms]) OR (causes[MeSH Terms]))
((lipedema[MeSH Terms]) AND ((pathophysiology[MeSH Terms]) OR (causes[MeSH Terms]))

INCLUSION CRITERIA

- Lower limb only
- Reviews
- Publication < 10 years, only ENG

SEARCH RESULT BEFORE - AFTER SELECTION

49 (before) - 15 (after selection)

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Westcott GP, Rosen ED. Crosstalk Between Adipose and Lymphatics in Health and Disease. *Endocrinology*. 2022 Jan 1;163(1):bqab224.
2. Rockson SG. Advances in Lymphedema. *Circ Res*. 2021 Jun 11;128(12):2003-2016.
3. Katzer K, et al. Lipedema and the Potential Role of Estrogen in Excessive Adipose Tissue Accumulation. *Int J Mol Sci*. 2021;22(21):11720.
4. Kruppa P, Georgiou I, Biermann N, et al. Lipedema-Pathogenesis, Diagnosis, and Treatment Options. *Dtsch Arztebl Int*. 2020;117(22-23):396-403.
5. Jiang X, Nicolls MR, Tian W, Rockson SG. Lymphatic Dysfunction, Leukotrienes, and Lymphedema. *Annu Rev Physiol*. 2018 Feb 10;80:49-70.
6. Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: A review of current literature. *Int Wound J*. 2018 Dec;15(6):921-928.
7. Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *J Clin Invest*. 2014 Mar;124(3):915-21
8. Farrow W. Phlebolympheidema. *J Am Col Certif Wound Spec*. 2010;2(1):14-23
9. Liu NF, Zhang LR. Changes of tissue fluid hyaluronan (hyaluronic acid) in peripheral lymphedema. *Lymphology*. 1998 Dec;31(4):173-9
10. Bates DO, Levick JR, Mortimer PS. Change in macromolecular composition of interstitial fluid from swollen arms after breast cancer treatment, and its implications. *Clin Sci (Lond)*. 1993 Dec;85(6):737-46.

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IDENTIFIED REFERENCES

(from the most recent down)

1. Westcott GP, Rosen ED. Crosstalk Between Adipose and Lymphatics in Health and Disease. *Endocrinology*. 2022;163(1):bqab224.
2. *Rockson SG. Advances in Lymphedema. *Circ Res*. 2021 Jun 11;128(12):2003-2016.
3. Brix B, Sery O, Onorato A, et al. Biology of Lymphedema. *Biology (Basel)*. 2021;10(4):261.
4. Katzer K, et al. Lipedema and the Potential Role of Estrogen in Excessive Adipose Tissue Accumulation. *Int J Mol Sci*. 2021;22(21):11720.
5. Kruppa P, Georgiou I, Biermann N, et al. Lipedema-Pathogenesis, Diagnosis, and Treatment Options. *Dtsch Arztebl Int*. 2020;117(22-23):396-403.
6. Wong KY, Furniss D. Current advances in lymphoedema management. *Br J Hosp Med* 2020;81(8):1-10
7. Jiang X, Nicolls MR, Tian W, Rockson SG. Lymphatic Dysfunction, Leukotrienes, and Lymphedema. *Annu Rev Physiol*. 2018 Feb 10;80:49-70.
8. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. *J Am Acad Dermatol*. 2017 Dec;77(6):1009-1020.
9. *Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: A review of current literature. *Int Wound J*. 2018 Dec;15(6):921-928.
10. Keeley V. Advances in understanding and management of lymphoedema (cancer, primary). *Curr Opin Support Palliat Care*. 2017 Dec;11(4):355-360.
11. Biglia N, Zanfagnin V, Daniele A, et al. Lower Body Lymphedema in Patients with Gynecologic Cancer. *Anticancer Res*. 2017;37(8):4005-4015.
12. Bakar Y, Tuğral A. Lower Extremity Lymphedema Management after Gynecologic Cancer Surgery. *Ann Vasc Surg*. 2017;44:442-450.
13. Iwersen LF, et al. Evidence-based practice in the management of lower limb lymphedema after gynecological cancer. *Physi Theory Pract*. 2017;33(1):1-8
14. Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *J Clin Invest*. 2014 Mar;124(3):915-21
15. Ridner SH. Pathophysiology of lymphedema. *Semin Oncol Nurs*. 2013;29(1):4-11

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 10, Statement 1, TOPIC: "LYMPHEDEMA & LIPEDEMA PATHO-PHYSIOLOGY"

Lymphedema is defined as an insufficiency in lymph drainage, due to vessel dysfunction and/or to an impairment in fluid generation, transport and outflow. It is characterized by a progressive accumulation of liquids in the interstitium. Differntely from what still too often believed, the liquid is not always protein-rich. **(Liu NF, Zhang LR. Changes of tissue fluid hyaluronan (hyaluronic acid) in peripheral lymphedema. Lymphology. 1998**

Dec;31(4):173-9) Lymphedema can be "primary" if mainly associated with a genetic background, or "secondary" if caused by a specific etiology compromising the lymphatic function (tissue damage, vessel obstruction or lymph nodes compromission.

***[Rockson SG. Advances in Lymphedema. Circ Res. 2021 Jun 11;128(12):2003-2016].**

Trauma, including surgery and lymphatic tissue dissection, infections and radiations are among the most common causes of secondary lymphedema. Lymphedema can be also the consequence of cardiac pump or renal failure.

[Brix B, Sery O, Onorato A, et al. Biology of Lymphedema. Biology (Basel). 2021;10(4):261]

A tight interconnection exists between veins and lymphatics functions, the two of them compensating each other, until an overload point in which the insufficiency of one can destabilize the other. Such condition in known as "phlebo-lymphedema".

[Farrow W. Phlebolymphedema-a common underdiagnosed and undertreated problem in the wound care clinic. J Am Col Certif Wound Spec. 2010;2(1):14-23]

Experts in the field are currently debating on the correlations between lymphedema and the so called "lipedema", discussing even the same nomenclature. This fat tissue alteration is characterized by symmetrical, disproportional distribution of fat deposited in the lower limbs and/or upper limbs of only women. Capillaries fragility in lipedema is testified by a tendency toward ecchymosis. Vein and lymphatics can be involved along the progression of the disease, configuring a mixed patho-physiology. While the lipedema pathophysiology details remain uncertain, a genetic component has been identified in up to 60% of cases. Fat hyperplasia and hypertrophy has been demonstrated, together with a tissue hypoxia that could explain the associated inflammatory state of these patients. Nevertheless, histopathology of lipedema remains not pathognomonic and further studies are encouraged.

***[Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: A review of current literature. Int Wound J. 2018;15(6):921-928].**

Lymphedema, phlebo-lymphedema and lipedema are too often underdiagnosed and poorly treated conditions, leading to chronic psycho-physical impairment, requiring expert management.

Further research is needed to define the patho-physiology aspects and intersections involved in lymphedema and lipedema development.

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 10, Statement 1

“Lymphedema is a chronic fluids accumulation. Lipedema is an inflammation of the leg fat tissue, possibly associated with lymphedema”

SELECTED REFEREENCES

1. *Rockson SG. Advances in Lymphedema. *Circ Res.* 2021 Jun 11;128(12):2003-2016[Brix B, Sery O, Onorato A, et al. *Biology of Lymphedema. Biology (Basel).* 2021;10(4):261
2. Brix B, Sery O, Onorato A, et al. *Biology of Lymphedema. Biology (Basel).* 2021;10(4):261
3. Farrow W. Phlebolymphe^dema-a common underdiagnosed and undertreated problem in the wound care clinic. *J Am Col Certif Wound Spec.* 2010;2(1):14-23
4. *Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: A review of current literature. *Int Wound J.* 2018;15(6):921-928. doi:10.1111/iwj.12949
5. Liu NF, Zhang LR. Changes of tissue fluid hyaluronan (hyaluronic acid) in peripheral lymphedema. *Lymphology.* 1998 Dec;31(4):173-9

identified LITERATURE BIAS

1. Possible mixture of venous, lymphatic and fat components in the pathophysiology investigations.

SUGGESTED NEXT LINES OF RESEARCH

1. Pure lipedema study models without lymphatic involvement
2. Pure venous study models without lymphatic involvement