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## Secondary Lymphatic Insufficiency in Chronic Varicose Veins

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To the Editor.

The interesting research of Sukiro et al.¹ offers an important contribution to understand the leg edema secondary to chronic venous stasis from varicose veins. Inside the pathophysiology of this complication, we recognize as relevant also the dysfunction of the lymphatic microcirculation. In fact, an increased pressure in the main venous trunks of the lower limbs directly reflects on the blood capillaries, favoring the leakage into the interstitial space of fluids, water, and solutes, but also of larger protein molecules, such as albumin, fibrinogen, and fibrin. Normally they move along 'low-resistance' ways, represented by the connective fibers of the interstitial tissue, toward the lymphatic capillaries. However, in condition of prolonged venous stasis, the abnormal amount of interstitial fluid and molecules exceeds the drainage capacity of this system, although in a first stage, the lymphatic capillaries enlarge, thanks to the compensatory mechanism activated by the stretched fibrils connected to their walls.²-⁴ Therefore, the pressure inside the lymphatic capillaries increases in a nonlinear relation, and beyond a physiological limit, hinders the lymph drainage. At the same time, the valves of the overloaded lymphatic precollectors lose their competence, further increasing the upstream congestion.⁵ This mechanism is self-feeding for the damage induced on the endothelial glycocalyx of the blood and lymphatic capillaries, which increase their permeability and the escape of large molecules. They, progressively accumulating in the interstitial tissue, decrease the osmotic gradient between capillaries and interstitial fluid.⁶ All these change the characteristics of the interstitial tissue environment, leading to an inflammatory-like condition, which becomes progressively more evident and irreversible.⁴¹ This cascade of pathological events outlines the edema as an important complication of the lower limb varicose veins. In the routine clinical practice, its evaluation can be performed through a careful study of t

## References

- 1. K. Suchiro, N. Morikage, T. Harada, et al., Extracellular fluid content in the legs of patients with chronic venous disease, Ann Vasc Surg 2020, https://doi.org/10.1016/j.avsq.2020.07.046.
- 2. J.W. Breslin, Y. Yang, J.P. Scallan, et al., Lymphatic vessel network structure and physiology, Compr Physiol 9, 2019, 207-299.
- 3. D. Negrini and A. Moriondo, Lymphatic anatomy and biomechanics, J. Physiol 589, 2011, 2927-2934.
- 4. H. Wiig and M.A. Swartz, Interstitial fluid and lymph formation and transport: physiological regulation and roles in inflammation and cancer, Physiol Rev 92, 2012, 1005-1060.
- 5. B.O. Ikhimwin, C.D. Bertram, S. Jamalian, et al., A computational model of a network of initial lymphatics and pre-collectors with permeable interstitium, Biomech Model Mechanobiol 19, 2020, 661-676.
- 6. O. Yilmaz, B. Afsar, A. Ortiz, et al., The role of endothelial glycocalyx in health an disease, Clin Kidney J 12, 2019, 611-619.
- 7. A. Caggiati, Ultrasonography of skin changes in legs with chronic venous disease, Eur J Vasc Endovasc Surg 52, 2016, 534-542.

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