

EVIDENCE BASED STATEMENT

DOMAIN **07**, Statement **01**
TOPIC: “**Venous Ulcer Pathophysiology**”

SEARCH TERMS & SOURCES

("Venos Ulcer"[Mesh] OR "Varicose Ulcer/pathology"[Mesh] OR "Venous Ulcer/physiopathology"[Mesh] OR "Venous Ulcer/physiopathology"[Mesh])

INCLUSION CRITERIA

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

SEARCH RESULT BEFORE - AFTER SELECTION

29 - 9

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Comerota, A., & Lurie, F. (2015). Pathogenesis of venous ulcer. *Seminars in vascular surgery*, 28(1), 6–14. <https://doi.org/10.1053/j.semvascsurg.2015.07.003>
2. Nicolaidis, A., Kakkos, S., Baekgaard, N., Comerota, A., de Maeseneer, M., Eklof, B., Giannoukas, A. D., Lugli, M., Maleti, O., Myers, K., Nelzén, O., Partsch, H., & Perrin, M. (2018). Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. *International angiology : a journal of the International Union of Angiology*, 37(3), 181–254. <https://doi.org/10.23736/S0392-9590.18.03999-8>
3. Nicolaidis, A., Kakkos, S., Baekgaard, N., Comerota, A., de Maeseneer, M., Eklof, B., Giannoukas, A., Lugli, M., Maleti, O., Mansilha, A., Myers, K. A., Nelzén, O., Partsch, H., & Perrin, M. (2020). Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part II. *International angiology : a journal of the International Union of Angiology*, 39(3), 175–240. <https://doi.org/10.23736/S0392-9590.20.04388-6>

EVIDENCE BASED STATEMENT

Domain 7; Statement 1

IDENTIFIED REFERENCES

1. Ortega, M. A., Fraile-Martínez, O., García-Montero, C., Álvarez-Mon, M. A., Chaowen, C., Ruiz-Grande, F., Pekarek, L., Monserrat, J., Asúnsolo, A., García-Honduvilla, N., Álvarez-Mon, M., & Bujan, J. (2021). Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. *Journal of clinical medicine*, *10*(15), 3239. <https://doi.org/10.3390/jcm10153239>
2. Raffetto, J. D., Ligi, D., Maniscalco, R., Khalil, R. A., & Mannello, F. (2020). Why Venous Leg Ulcers Have Difficulty Healing: Overview on Pathophysiology, Clinical Consequences, and Treatment. *Journal of clinical medicine*, *10*(1), 29. <https://doi.org/10.3390/jcm10010029>
3. Nicolaidis A. N. (2020). The Most Severe Stage of Chronic Venous Disease: An Update on the Management of Patients with Venous Leg Ulcers. *Advances in therapy*, *37*(Suppl 1), 19–24. <https://doi.org/10.1007/s12325-020-01219-y>
4. Raffetto J. D. (2018). Pathophysiology of Chronic Venous Disease and Venous Ulcers. *The Surgical clinics of North America*, *98*(2), 337–347. <https://doi.org/10.1016/j.suc.2017.11.002>
5. Mansilha, A., & Sousa, J. (2018). Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. *International journal of molecular sciences*, *19*(6), 1669. <https://doi.org/10.3390/ijms19061669>
6. Lim, C. S., Baruah, M., & Bahia, S. S. (2018). Diagnosis and management of venous leg ulcers. *BMJ (Clinical research ed.)*, *362*, k3115. <https://doi.org/10.1136/bmj.k3115>
7. Santler, B., & Goerge, T. (2017). Chronic venous insufficiency - a review of pathophysiology, diagnosis, and treatment. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *15*(5), 538–556. <https://doi.org/10.1111/ddg.13242>
8. Crawford, J. M., Lal, B. K., Durán, W. N., & Pappas, P. J. (2017). Pathophysiology of venous ulceration. *Journal of vascular surgery. Venous and lymphatic disorders*, *5*(4), 596–605. <https://doi.org/10.1016/j.jvsv.2017.03.015>
9. Zhao, R., Liang, H., Clarke, E., Jackson, C., & Xue, M. (2016). Inflammation in Chronic Wounds. *International journal of molecular sciences*, *17*(12), 2085. <https://doi.org/10.3390/ijms17122085>

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 01, Statement 01, TOPIC: “**Venous Ulcer Pathophysiology**”

Venous ulceration represents the severe ending of a not properly managed lower limb venous hypertension, generated by genetic and/or environmental factors. The hemodynamic impairment can be caused by a vein obstruction and/or reflux whose mechanical force is translated into biochemical inflammatory messages leading to tissue damage. The inflammatory process is associated with alteration of the proteolytic activity and with tissue fibrosis and is usually anticipated by the lipodermatosclerosis condition.

[Raffetto JD. Inflammation in chronic venous ulcers. Phlebology. 2013 Mar;28 Suppl 1:61-7].

The vessel wall and valves integrity loss represent a fundamental pathophysiological aspect in the ulceration process, as particularly evident in case of thrombotic processes. Another fundamental player in venous ulceration is the calf pump function, whose decreased performance has been found to be associated with the same wound presence.

[Araki CT, Back TL, Padberg FT, et al. The significance of calf muscle pump function in venous ulceration. J Vasc Surg. 1994 Dec;20(6):872-7]

Whatever condition is altering the vessel wall elasticity (capacitance), the venous drainage propulsion (conductivity) and/or the vein patency (resistance) might lead to venous hypertension and related ulceration. Genetic mutations can expose the patient to an easier tissue damage and/or to a more cumbersome reparation. In this context, iron metabolism and metalloproteases balance demonstrated a pivotal role.

[Raffetto JD, Ligi D, Maniscalco R, et al. Why Venous Leg Ulcers Have Difficulty Healing: Overview on Pathophysiology, Clinical Consequences, and Treatment. J Clin Med. 2020 Dec 24;10(1):29].

Different pathophysiology theories have been proposed along the years, yet missing complete evidence-based validation. Among these, the venous stasis theory proposed the hypoxia role. The arteriovenous fistula hypothesis report the shunting of oxygen and nutrients as triggering factor. Fibrin cuff and white blood cell trap theory focused on the venous hypertension role in extravasation of fibrinogen and white blood cell activation, respectively. In conclusion, venous ulcer pathophysiology is still in need of translational medicine investigations to clarify the complex process connecting the venous drainage compromise with the wound generation.

***[Comerota A, Lurie F. Pathogenesis of venous ulcer. Semin Vasc Surg. 2015 Mar;28(1):6-14].**

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 7, Statement 1

“Approximately 70% of skin ulcer has a venous origin. 1/5 ulcers have a multi-factorial component that has to be investigated”

SELECTED REFERENCES

1. Raffetto JD. Inflammation in chronic venous ulcers. *Phlebology*. 2013 Mar;28 Suppl 1:61-7
2. Araki CT, Back TL, Padberg FT, et al. The significance of calf muscle pump function in venous ulceration. *J Vasc Surg*. 1994 Dec;20(6):872-7
3. Raffetto JD, Ligi D, Maniscalco R, et al. Why Venous Leg Ulcers Have Difficulty Healing: Overview on Pathophysiology, Clinical Consequences, and Treatment. *J Clin Med*. 2020 Dec 24;10(1):29
4. *Comerota A, Lurie F. Pathogenesis of venous ulcer. *Semin Vasc Surg*. 2015 Mar;28(1):6-14

identified LITERATURE BIAS

Reflux time as only hemodynamic parameter to quantify the reflux severity

SUGGESTED NEXT LINES OF RESEARCH

Correlation between hemodynamic impairment objective parameters and inflammatory markers