

EVIDENCE BASED STATEMENT

DOMAIN **07**, Statement **9**

TOPIC: “**Skin grafting, negative pressure therapy, stem cells therapy evidence-based state of the art**”

SEARCH TERMS & SOURCES

(skin grafting) AND (venous ulcer) ; (negative pressure) AND (venous ulcer) ; (stem cells) AND (venous ulcer)

INCLUSION CRITERIA

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

SEARCH RESULT BEFORE - AFTER SELECTION

60/12

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Falanga V, Grada A, Otero-Vinas M, et al. Autologous Cultured Bone Marrow-Derived Mesenchymal Stem Cells in a Fibrin Spray to Treat Venous Ulcers: A Randomized Controlled Double-Blind Pilot Study. Surg Technol Int. 2022 May 19;40:47-54.
2. Kirsner RS, Zimnitsky D, Robinson M. A prospective, randomized, controlled clinical study on the effectiveness of a single-use negative pressure wound therapy system, compared to traditional negative pressure wound therapy in the treatment of diabetic ulcers of the lower extremities. Wound Repair Regen. 2021 Nov;29(6):908-911.
3. Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. Wounds. 2019 Mar;31(3):68-74.

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IDENTIFIED REFERENCES

1. Dong Y, Yang Q, Sun X. Comprehensive Analysis of Cell Therapy on Chronic Skin Wound Healing: A Meta-Analysis. *Hum Gene Ther.* 2021 Aug;32(15-16):787-795.
2. Ren SY, Liu YS, Zhu GJ, et al. Strategies and challenges in the treatment of chronic venous leg ulcers. *World J Clin Cases.* 2020 Nov 6;8(21):5070-5085.
3. Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev.* 2013 Jan 31;2013(1):CD001737.
4. Aleksandrowicz H, Owczarczyk-Saczonek A, Placek W. Venous Leg Ulcers: Advanced Therapies and New Technologies. *Biomedicines.* 2021 Oct 29;9(11):1569.
5. Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database Syst Rev.* 2015 Jul 14;2015(7):CD011354.
6. Elsharkawi M, Ghoneim B, Westby D, Jones D, Tawfick W, Walsh SR. Adipose-derived stem cells in patients with venous ulcers: Systematic review. *Vascular.* 2022 May 1:17085381221098279.
7. Ren SY, Liu YS, Zhu GJ, et al. Strategies and challenges in the treatment of chronic venous leg ulcers. *World J Clin Cases.* 2020 Nov 6;8(21):5070-5085.
8. Zollino I, Campioni D, Sibilla MG, et al. A phase II randomized clinical trial for the treatment of recalcitrant chronic leg ulcers using centrifuged adipose tissue containing progenitor cells. *Cytotherapy.* 2019 Feb;21(2):200-211.
9. Shao M, Hussain Z, Thu HE, et al. Emerging Trends in Therapeutic Algorithm of Chronic Wound Healers: Recent Advances in Drug Delivery Systems, Concepts-to-Clinical Application and Future Prospects. *Crit Rev Ther Drug Carrier Syst.* 2017;34(5):387-452.
10. Athanerey A, Patra PK, Kumar A. Mesenchymal stem cell in venous leg ulcer: An intoxicating therapy. *J Tissue Viability.* 2017 Aug;26(3):216-223.
11. Zollino I, Zuolo M, Gianesini S, et al. Autologous adipose-derived stem cells: Basic science, technique, and rationale for application in ulcer and wound healing. *Phlebology.* 2017 Apr;32(3):160-171.
12. Akita S, Yoshimoto H, Akino K, et al. Early experiences with stem cells in treating chronic wounds. *Clin Plast Surg.* 2012 Jul;39(3):281-92.

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 07, Statement 9, TOPIC: “**Skin grafting, negative pressure therapy, stem cells therapy evidence-based state of the art**”

The pivotal initial treatment of venous ulcers includes wound care, debridement, appropriate life-style and compression, In case of delayed healing, after 4-6 weeks, advanced options might be taken into consideration, among which skin grafting, negative pressure therapy and stem cells from adipose tissue or placenta injection. Autologous platelet-rich plasma and other blood derived components are proposed as well. All these options, while potentially beneficial, are lacking solid scientific data for which their indication is still left to the evaluation of the single case and in need of proper evidence-based validation.

[Ren SY, Liu YS, Zhu GJ, et al. Strategies and challenges in the treatment of chronic venous leg ulcers. World J Clin Cases. 2020 Nov 6;8(21):5070-5085]

Skin substitutes showed potentials in reducing mortality and lessen morbidity while improving quality of life. Yet no commercially available products have recent sufficient scientific validation to be recommended, up to the knowledge of the authors.

[Dearman BL, Boyce ST, Greenwood JE. Advances in Skin Tissue Bioengineering and the Challenges of Clinical Translation. Front Surg. 2021 Aug 24;8:640879].

Innovative therapeutic options of this kind are still in need of properly conducted randomized comparative trials.

***[Aleksandrowicz H, Owczarczyk-Saczonek A, Placek W. Venous Leg Ulcers: Advanced Therapies and New Technologies. Biomedicines. 2021 Oct 29;9(11):1569].**

A 2022 review identified just four papers, of which just one randomized comparative trial, investigating the use of adipose derived stem cells in venous ulcer healing. This therapeutic approach may enhance ulcer healing and appears to be safe on initial reports. Nevertheless, more solid publications are needed, including the safety profile, before recommending this wound therapy.

[Elsharkawi M, Ghoneim B, Westby D, et al. Adipose-derived stem cells in patients with venous ulcers: Systematic review. Vascular 2022]

Also for negative pressure therapy use in venous ulcer healing there is limited rigorous evidence. Mild evidence suggest it can reduce the healing time, yet the result is biased by the very specific lesions type included in the investigations.

[Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. Cochrane Database Syst Rev. 2015 Jul 14;2015(7):CD011354].

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 7, Statement 9

Skin grafting, Negative Pressure Therapy, Stem cells therapy can be valuable options in specific cases assessed by experts, but more scientific evidence is needed for supporting their use

SELECTED REFERENCES

1. Ren SY, Liu YS, Zhu GJ, et al. Strategies and challenges in the treatment of chronic venous leg ulcers. *World J Clin Cases*. 2020 Nov 6;8(21):5070-5085
2. Dearman BL, Boyce ST, Greenwood JE. Advances in Skin Tissue Bioengineering and the Challenges of Clinical Translation. *Front Surg*. 2021 Aug 24;8:640879
3. Aleksandrowicz H, Owczarczyk-Saczonek A, Placek W. Venous Leg Ulcers: Advanced Therapies and New Technologies. *Biomedicines*. 2021 Oct 29;9(11):1569
4. Elsharkawi M, Ghoneim B, Westby D, et al. Adipose-derived stem cells in patients with venous ulcers: Systematic review. *Vascular* 2022
5. Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database Syst Rev*. 2015 Jul 14;2015(7):CD011354

identified LITERATURE BIAS

Specific ulcer types evaluation with limited number of cases

SUGGESTED NEXT LINES OF RESEARCH

Large multi-center randomized trial on head to head comparison