GMR
The Original

Inflammatory and Genetic Mechanisms Underlying Chronic Venous Ulcer Healing: Translational Insights from a CEAP 6 Limb Salvage Case

Juan Carlos Navarrete Pérez [1*], Diana Carolina Flórez Pastrana [2], Maite Belén Calderon Torres [3], María Camila Jacome Gallardo [4], María Alejandra Moya Almeida [5], Estefano Danilo Cruz Gallo [6], Mateo Enrique Rojas Salazar [7], Tania Belen Oña Velasque [8], Dennis Jair Huilcatoma Salazar [9]

[1,3,4,5,6,7,8,9] Universidad de las Américas-UDLA Medicina/Pichincha- Quito, Ecuador
[2] Universidad Surcolombiana-Medicina, Huila-Neiva, Colombia

[*]**Corresponding Author**: dr.juancanap@gmail.com

ABSTRACT

Background: Chronic venous disease, particularly in CEAP stage 6 (active venous ulcers), represents a significant therapeutic challenge with a high risk of amputation, especially in patients with comorbidities such as diabetes and a history of contralateral amputation. **Objective:** Analyze the comprehensive clinical and surgical approach applied for the successful salvage of a lower limb, which was initially considered non-viable, in a patient with a history of contralateral amputation due to chronic venous insufficiency with advanced ulceration, highlighting the importance of multidisciplinary management. **Method:** A descriptive, retrospective case study was conducted on a 67-year-old woman with type 2 diabetes and a bilateral venous ulcer classified as CEAP 6. Following initial right supracondylar amputation, a salvage strategy was chosen for the left limb. Management included surgical debridement, antibiotics targeted by culture to Staphylococcus aureus, radiofrequency ablation of the great saphenous vein, and a distal endovascular technique, followed by an advanced wound care regimen with bacteriostatic and hydrocolloid dressings. **Results:** Despite the initial indication for bilateral amputation, the left lower limb showed favorable progression. Surgical management and advanced wound therapy led to bone exposure coverage and complete re-epithelialization of the ulcer within three months of outpatient follow-up. **Conclusions:** The successful salvage of the lower limb in this case underscores that CEAP 6 chronic venous insufficiency, even in high-risk scenarios such as a history of contralateral amputation, can be effectively treated through early diagnosis with venous Doppler ultrasound and a combined therapeutic strategy that includes venous and arterial intervention, strict control of comorbidities, and a rigorous regimen of advanced wound care.

Keywords: *Chronic venous insufficiency, Venous leg ulcer, Inflammatory cytokines, Wound healing mechanisms, Genetic susceptibility*

INTRODUCTION

Chronic venous disease (CVD) is defined as the presence of persistent structural and/or functional abnormalities in the venous system, accompanied by signs and symptoms that warrant medical evaluation

(Youn & Lee, 2019; De Maeseneer et al., 2022). Its pathophysiology is complex due to the involvement of multiple factors, affecting the superficial and deep venous systems, soft tissues, and the microcirculation (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

The formation of varicose veins is associated with several risk factors, most of which are non-modifiable and often coexist in the same individual. These include a family history of chronic venous insufficiency, advanced age, female sex, prior episodes of deep vein thrombosis or pulmonary embolism, multiple pregnancies, the presence of lipodermatosclerosis, and certain musculoskeletal or joint disorders (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

There are also potentially modifiable factors contributing to venous disease, such as overweight, obesity, and sedentary lifestyle. Additionally, some genetic determinants may increase susceptibility, likely following an autosomal dominant pattern with variable expression. Although no specific causative gene has been identified, the Forkhead box C2 (FOXC2) gene region, located on chromosome 16q24, has been suggested as a potential marker associated with increased risk of varicose vein development (Robles-Tenorio & Ocampo-Candiani, 2022).

In the superficial venous system, inflammatory processes may induce structural changes in the vascular wall, including degradation of elastin and collagen fibers, leading to valvular incompetence and venous reflux (Youn & Lee, 2019).

A case-control study examined clinical factors associated with the development of venous ulcers in patients with lower extremity varices, comparing 70 individuals with a history of venous ulcers to 1,164 patients with varices without ulcerative complications. Multivariable analysis identified several conditions significantly associated with an increased risk of ulceration, including male sex, overweight and obesity, prolonged duration of varicose veins, deep venous system valvular dysfunction, reduced lymphocyte levels, and elevated plasma fibrinogen (Yin et al., 2024).

In the deep venous system, normal flow may be disrupted by obstruction and/or reflux related to external compression or deep vein thrombosis. Recanalization of a deep vein thrombosis may result in valvular damage and venous reflux, whereas obstruction without recanalization can cause venous hypertension in superficial veins (Youn & Lee, 2019).

At the microcirculatory level in soft tissues, venous hypertension leads to dilation of small veins and venules, resulting in incompetence and leakage of inflammatory mediators and cells, which triggers inflammation, fibrosis, hypoxia, and disruption of normal skin architecture (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

At the cellular level, endothelial activation induces the expression of adhesion molecules such as ICAM-1, VCAM-1, and E-selectins, recruiting inflammatory cells and increasing inflammatory and proteolytic mediators. These processes contribute to myofibroblast differentiation, vascular wall remodeling, increased vascular permeability, and soft tissue degradation, promoting venous ulcer formation (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

Wound healing is a dynamic process occurring within an inflammatory environment, involving multiple cell types and cytokines. Cytokine deficiency has been shown to adversely affect this process; however, in the context of venous ulcers, the inflammatory environment becomes unfavorable, delaying tissue repair. In this context, the question arises regarding which specific inflammatory mediators hinder venous ulcer healing (Coelho et al., 2023; Burian et al., 2022). A systematic review analyzing 28 studies and

investigating 38 cytokines in 790 patients with both healing and non-healing venous ulcers found that persistent ulcers were associated with elevated levels of IL-1α, IL-6, IL-8, TNF-α, and vascular endothelial growth factor (VEGF). These levels tended to decrease as healing progressed, whereas transforming growth factor beta 1 (TGF-β1) increased during tissue repair. Nonetheless, these findings should be interpreted cautiously due to moderate-to-high methodological bias and the presence of inconsistent or statistically non-significant results (Burian et al., 2022).

The development of varicose veins is linked to multiple risk factors, most of which are non-modifiable and frequently coexist in the same patient. These include a family history of chronic venous insufficiency, aging, female sex, prior episodes of deep vein thrombosis or pulmonary embolism, multiple pregnancies, lipodermatosclerosis, and musculoskeletal or joint disorders (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

Moreover, modifiable factors such as overweight, obesity, and sedentary lifestyle also contribute to venous disease. Certain genetic variants may further increase susceptibility, likely following an autosomal dominant pattern with variable expression. While no causative gene has been definitively identified, the FOXC2 gene region on chromosome 16q24 has been proposed as a potential marker associated with predisposition to varicose vein development (Robles-Tenorio & Ocampo-Candiani, 2022).

A case-control study evaluated clinical factors that may promote venous ulcer formation in patients with lower extremity varices. Two groups were compared: 70 patients with a history of venous ulcers and 1,164 patients with varices without ulcerative complications. Multivariable analysis identified several conditions associated with a significantly higher risk of developing ulcerations, including male sex, overweight and obesity, prolonged varicose vein duration, deep venous valvular dysfunction, reduced lymphocyte counts, and elevated fibrinogen levels (Yin et al., 2024).

Clinical evaluation should include a detailed history of thromboembolic events, allergies, and assessment of venous symptoms. Patients often report pruritus with or without visible skin lesions, dull pain in the calf region, foot edema at the end of the day, and nocturnal cramps (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

On physical examination in the early stages of chronic venous disease, telangiectasias and reticular veins are commonly observed. As the disease progresses, more advanced signs may appear, including prominent varices, brown or orange skin pigmentation, persistent lower limb edema, stasis dermatitis, atrophic skin areas, and lipodermatosclerosis (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

Venous ulcers typically localize to the distal leg, particularly the medial region, and present as superficial lesions with irregular but well-defined edges, with fibrinous tissue at the wound base (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022). These findings are documented and organized using the CEAP classification (clinical, etiologic, anatomic, and pathophysiologic), which serves both for treatment guidance and research purposes (Youn & Lee, 2019; De Maeseneer et al., 2022).

Although venous ulcers are the most common form of chronic lower extremity ulcers, other etiologies must be considered in the differential diagnosis, including occlusive arterial disease, mixed venous-arterial involvement, diabetic neuropathic ulcers, malignant lesions, pyoderma gangrenosum, and other inflammatory conditions (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

In all patients with suspected venous ulcers, non-invasive imaging studies are recommended, including comprehensive venous ultrasonography, peripheral arterial pulse assessment, and ankle-brachial index

measurement to identify or rule out concomitant arterial disease (Youn & Lee, 2019; De Maeseneer et al., 2022; Robles-Tenorio & Ocampo-Candiani, 2022).

Objective

To analyze the clinical and surgical approach applied for the successful salvage of the lower limb in a patient with a history of contralateral limb amputation due to chronic venous insufficiency and active ulceration, emphasizing the importance of comprehensive multidisciplinary management.

Specific objectives

- To identify the clinical and surgical factors that increase the likelihood of amputation in patients with chronic venous ulcers.

- To analyze the clinical and surgical management, including comorbidity control, the surgical technique employed, and advanced wound healing strategies that contribute to successful limb salvage.

MATERIALS AND METHOD

This study consists of the description of a clinical case. A qualitative approach was employed, using amputation scales and criteria to assess qualitative aspects, complemented by quantitative tools that allowed for the evaluation of infection severity and lesion extent. Simultaneously, additional quantitative analyses were performed. A descriptive, retrospective case study was conducted, focusing on the clinical and surgical management of patients with chronic venous insufficiency classified as CEAP 6.

The data were obtained from the patient's medical record at IESS Quito Sur Hospital, allowing the collection of information regarding her care in the Emergency Department, operating room, and hospitalization, as well as details about the treatment received, clinical progression, and subsequent follow-up.

RESULTS

We report the case of a 67-year-old woman, without formal education, a housewife, right-handed, and of Catholic faith, with no history of allergies, who denies tobacco and alcohol use but has had approximately 45 years of exposure to wood smoke. She reports no prior blood transfusions. Her medical history is significant for chronic degenerative diseases, including type II diabetes mellitus diagnosed 10 years ago, treated with metformin 500 mg orally once daily, with no prior surgical history.

The patient was admitted to the emergency department and subsequently transferred to vascular surgery due to the presence of bilateral vascular ulcers on the lower extremities with a 10-year course, previously managed at a health center. However, three months before admission, she experienced increased pain and the onset of malodorous seropurulent discharge.

Physical Examination:

Upon admission, the elderly patient appeared normosomic, with intact cognitive function, fully oriented, well-hydrated, afebrile, and normotensive.
Vital signs: BP 135/80 mmHg, HR 75 bpm, RR 18/min, temperature 36.5 °C.
Weight: 70 kg; height: 168 cm; BMI: 24.8 kg/m².

Examination of the head, neck, thorax, abdomen, and upper extremities revealed no abnormalities. The

lower extremities were symmetrical, with dry skin, pitting edema +/++++, eutermic, distal color changes, capillary refill <3 seconds, and palpable femoral, popliteal, and distal pulses ++/++.

In the right lower limb, a 25 x 40 cm ulcer with regular borders was observed, involving soft tissue and bone, with exposure of the distal third of the fibula, moderate eschar tissue, and minimal malodorous serous discharge. On the dorsum of the right foot, two ulcers measuring 2 x 4 cm and 2 x 5 cm with regular borders and fibrinous bases were identified.

In the left lower limb, there was a 25 x 25 cm ulcer with irregular borders affecting soft tissue and bone, exposing the distal third of the tibia, moderate eschar tissue, and minimal malodorous discharge. Additionally, an 8 x 8 cm ulcer was present on the lateral aspect of the middle third of the leg, with regular borders, fibrinous base, and moderate eschar tissue.

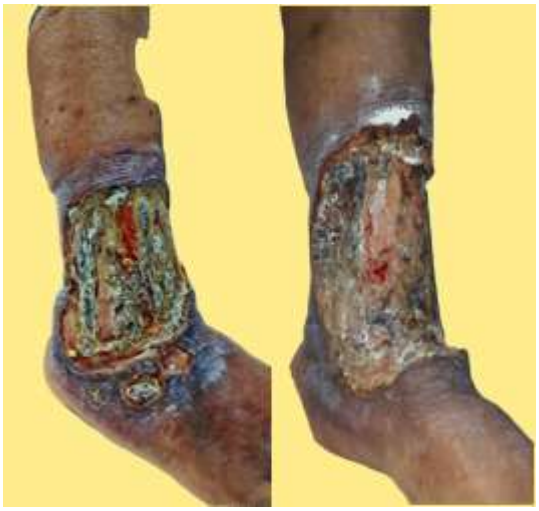

Figure 1: Right and left lower limbs showing the findings described.

Consolidated Laboratory Results:

- 08/05/2025: WBC 9.21 (4–10 x10³/µL), Neutrophils 77% (40–70%), Hemoglobin 11.4 (12–16 g/dL), Hematocrit 35.5 (36–46%), Platelets 431 (150–450 x10³/µL), Glucose 132 (70–100 mg/dL), HbA1c 6.8% (<5.7%), Urea 22.9 (17–43 mg/dL), Creatinine 0.63 (0.6–1.2 mg/dL), Total Proteins 6.2 (6–8 g/dL), Albumin 3.3 (3.5–5 g/dL), Globulin 2.9 (2–3.5 g/dL), A/G Ratio 1.14 (1–2), Triglycerides 124 (<150 mg/dL), Cholesterol 158 (<200 mg/dL), HDL 36.4 (>40 mg/dL), LDL 96.8 (<100 mg/dL), Total Bilirubin 0.82 (0.3–1.2 mg/dL), Direct Bilirubin 0.33 (0–0.3 mg/dL), Indirect Bilirubin 0.49 (0.2–0.8 mg/dL), AST/TGO 34 (10–40 U/L), ALT/TGP 25 (7–56 U/L), Sodium 139 (135–145 mmol/L), Potassium 3.89 (3.5–5.1 mmol/L), Chloride 106 (98–107 mmol/L), TSH 6.89 (0.4–4.5 µIU/mL), FT4 1.47 (0.8–1.8 ng/dL).

- 09/05/2025 POST-TRANSFUSION: WBC 8.12 (4–10 x10³/µL), Neutrophils 75.9% (40–70%), Hemoglobin 11.1 (12–16 g/dL), Hematocrit 33.6 (36–46%), Platelets 387 (150–450 x10³/µL).

- 09/07/2025: WBC 9.06 (4–10 x10³/µL), Neutrophils 73.8% (40–70%), Hemoglobin 8.7 (12–16 g/dL), Hematocrit 27.1 (36–46%), Platelets 372 (150–450 x10³/µL), PT 12.4 (11–13.5 s), INR 1.14

(0.8–1.2), aPTT 33.7 (25–35 s), Glucose 189 (70–100 mg/dL), Urea 39.4 (17–43 mg/dL), Creatinine 0.6 (0.6–1.2 mg/dL), Sodium 141 (135–145 mmol/L), Potassium 4.22 (3.5–5.1 mmol/L), Chloride 111 (98–107 mmol/L), High-sensitivity CRP 9.98 (<0.5 mg/dL), Procalcitonin 0.05 (<0.1 ng/mL).

Treatment:

Following preoperative assessment by the clinical services and consensus between trauma and plastic surgery teams, it was determined that, due to the type and extent of the lesion, the limb was non-viable, and a bilateral above-knee amputation was initially recommended. After obtaining informed consent and providing a detailed explanation to the patient and her family, a right above-knee amputation was performed without complications. In the subsequent days, amputation of the left limb was planned; however, the possibility of attempting limb salvage was discussed with the patient, who consented to this approach.

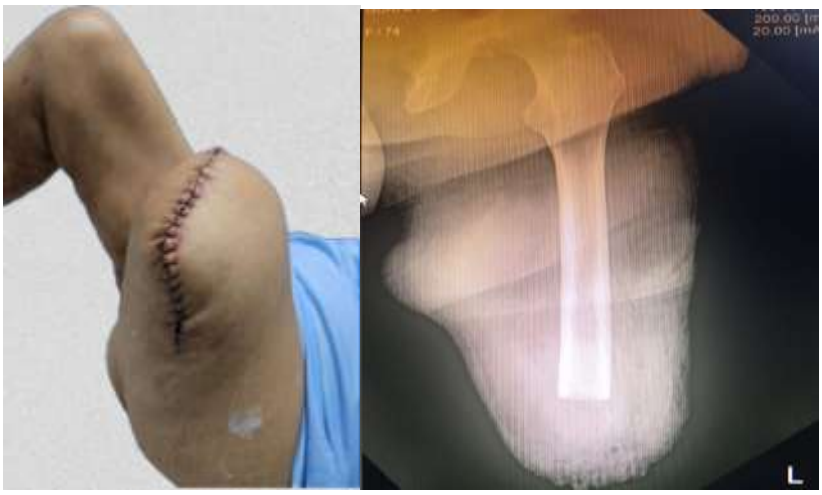

Figure 2: On the left, the postoperative left limb stump is shown, along with an X-ray of the anterior stump.

The patient remained hospitalized, receiving a broad-spectrum antibiotic regimen guided by a positive culture for multisensitive Staphylococcus aureus. Hemodynamic stability was managed in the context of mild to moderate post-surgical anemia. On the eighth postoperative day, surgical debridement with radiofrequency ablation of the left great saphenous vein and distal endovascular intervention was planned, along with culture collection; the procedure was completed without complications. Wound care was performed using bacterial-adhesive dressings every 48 hours, combined with bedside irrigation with normal saline. Laboratory follow-up showed no inflammatory response, asymptomatic moderate anemia, vital signs within normal limits, and controlled pain, leading to patient discharge with scheduled outpatient follow-up for vascular ulcer care.

Figure 3. Limb post-surgical debridement with radiofrequency ablation of the left great saphenous vein and distal endovascular technique.

On an outpatient basis, advanced dressings were performed every six days, including mechanical debridement of slough tissue for three weeks, along with the application of bacterially adherent dressings. The ulcer bed showed no signs of infection, minimal slough tissue, and areas of granulation tissue, with exposure of the distal third of the fibula. Subsequently, a thick hydrocolloid dressing was applied for four weeks, showing favorable progression with the development of hypergranulation tissue and coverage of the bone. This was followed by a thin hydrocolloid dressing for four weeks, demonstrating progressive epithelialization and achieving complete healing by the third month.

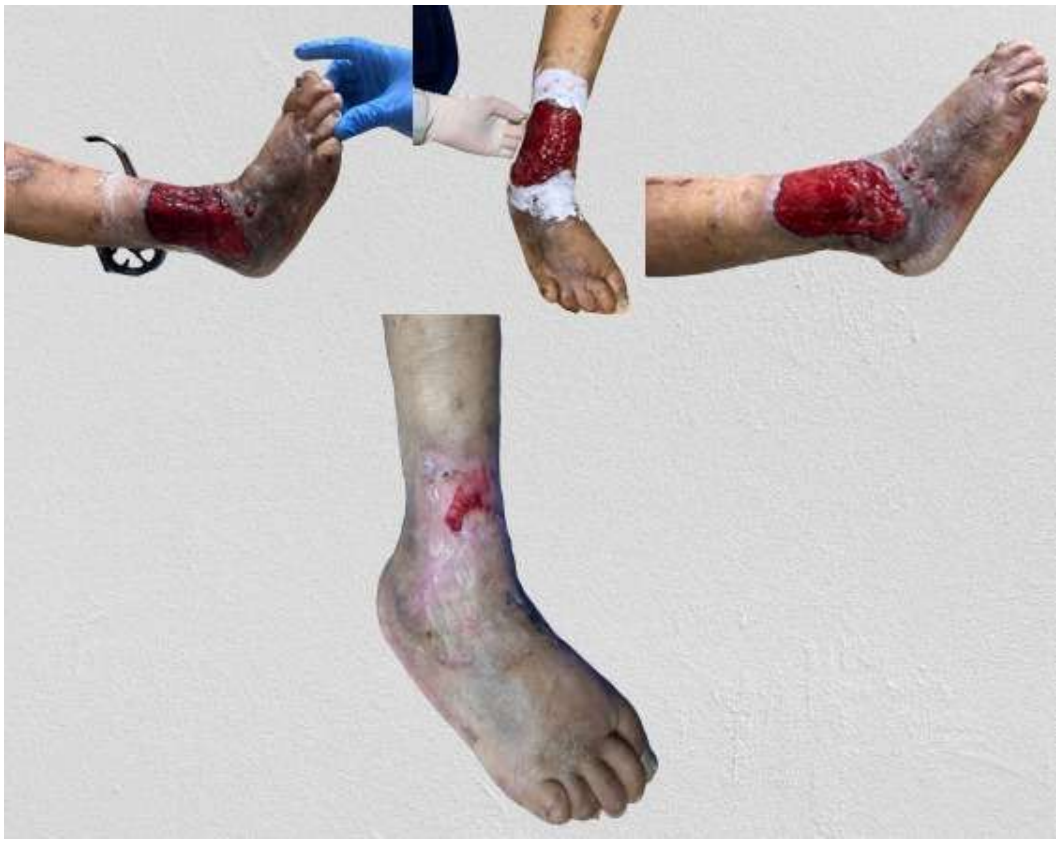

Figure 4. Natural progression of the affected limb with weekly dressings, showing the final outcome of the ulcer fully re-epithelialized and in good condition.

DISCUSSION:

Venous ulcers affect approximately 1% of the general population, increasing up to 3% in individuals over 80 years old. It is estimated that around 93% of these lesions close within 12 months, although approximately 7% remain unhealed even after five years. It is important to note that these figures may overestimate outcomes in routine clinical practice. Recurrence after initial healing is also high, with rates reaching up to 70% within the first three months after wound closure (Vuylsteke et al., 2018).

Conservative management of venous ulcers primarily involves two components: direct wound care and compression therapy (Robles-Tenorio & Ocampo-Candiani, 2022). Additionally, patient management should be comprehensive, including control of comorbidities, physiotherapy, and mobilization, aiming to restore quality of life (Youn & Lee, 2019).

Direct wound care entails the removal of necrotic tissue, cellular debris, or foreign bodies. Cleaning should be performed with non-toxic agents to preserve viable tissue, followed by debridement, which can be surgical, mechanical, enzymatic, or autolytic. Dressings serve key functions: maintaining adequate moisture, protecting the wound, and promoting granulation and re-epithelialization (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022). A Cochrane meta-analysis showed that sucralfate and silver dressings may offer some advantage in venous ulcer healing; however, due to low certainty of evidence, no

specific dressing type is recommended over another. Clinicians should also consider other patient-centered factors such as preference and cost (Norman et al., 2018).

For venous ulcers with foul odor, purulent discharge, or poor healing, tissue sampling for culture is recommended rather than superficial swabbing, to appropriately guide antimicrobial therapy (Robles-Tenorio & Ocampo-Candiani, 2022).

Superimposed mechanical compression is primarily indicated for small venous ulcers. This system consists of an inner stocking that secures the dressing and is only removed during dressing changes, providing continuous pressure of approximately 20 mmHg, tolerable even in the supine position. During the day, a second stocking is added, exerting an additional 20–25 mmHg, generating total compression of around 40 mmHg at rest and up to 50 mmHg while standing, which promotes healing. Cochrane reviews indicate that multicomponent elastic systems achieve better healing rates than single-layer systems (Youn & Lee, 2019; Robles-Tenorio & Ocampo-Candiani, 2022).

Surgical and endovascular management of superficial veins in patients with venous ulcers aims to prevent recurrence. Minimally invasive endovascular interventions are currently preferred over open surgery. However, the 2022 Clinical Practice Guidelines of the European Society for Vascular Surgery recommend that the choice of procedure should be guided by the surgeon's expertise and the patient's characteristics and preferences (De Maeseneer et al., 2022).

CONCLUSION

Chronic venous insufficiency (CVI) in its most advanced stage (CEAP 6) necessitates an assertive and timely diagnostic and therapeutic approach to avert disability and major amputation. In this context, venous Doppler ultrasound is imperative as a primary instrument for characterizing vascular morphology and flow dynamics, thereby guiding the planning of interventions. The case presented herein demonstrates that successful limb salvage is feasible through a synergistic clinical-surgical strategy, even in high-risk patients with a history of contralateral amputation (e.g., the diabetic patient). The following elements should be incorporated into the strategy: First, rigorous control of comorbidities (e.g., diabetes) is imperative. Second, a combined intervention is necessary to treat the venous etiology (radiofrequency ablation) and peripheral arterial disease (distal endovascular intervention). Third, advanced, protocolized wound management with constant debridement and sequential use of advanced dressings (bacterioadhesive and hydrocolloids) to achieve complete healing is essential. This positive outcome, which was accomplished without the necessity for intricate surgical interventions such as flaps or skin grafts and in an ambulatory care setting, lends further support to the prevailing literature that advocates for a multidisciplinary approach to limb preservation, even in cases where initial indications suggest amputation.

REFERENCES

Youn, Y. J., & Lee, J. (2019). Chronic venous insufficiency and varicose veins of the lower extremities. *Korean Journal of Internal Medicine, 34*(2), 269–283. https://pmc.ncbi.nlm.nih.gov/articles/PMC6406103/

De Maeseneer, M. G., Kakkos, S. K., Aherne, T., Baekgaard, N., Black, S., Blomgren, L., et al. (2022). European Society for Vascular Surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. *European Journal of Vascular and Endovascular Surgery, 63*(2), 184–267. https://www.ejves.com/action/showFullText?pii=S1078588421009795

Coelho, G. A., Secretan, P. H., Tortolano, L., Charvet, L., & Yagoubi, N. (2023). Evolution of the chronic venous leg ulcer microenvironment and its impact on medical devices and wound care therapies. *Journal of Clinical Medicine, 12*(17), 5605. https://pmc.ncbi.nlm.nih.gov/articles/PMC10488485/

Burian, E. A., Sabah, L., Karlsmark, T., Kirketerp-Møller, K., Moffatt, C. J., & Thyssen, J. P. (2022). Cytokines and venous leg ulcer healing: A systematic review. *International Journal of Molecular Sciences, 23*(12), 6526. https://pmc.ncbi.nlm.nih.gov/articles/PMC9224200/

Robles-Tenorio, A., & Ocampo-Candiani, J. (2022). Venous leg ulcer. In *Phlebology, vein surgery and ultrasonography: Diagnosis and management of venous disease* (pp. 341–353). StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK567802/

Vuylsteke, M. E., Colman, R., Thomis, S., Guillaume, G., Van Quickenborne, D., & Staelens, I. (2018). An epidemiological survey of venous disease among general practitioner attendees in different geographical regions on the globe: Final results of the vein consult program. *Angiology, 69*(9), 779–785. https://doi.org/10.1177/0003319718759834

Yin, C., Tang, F., Lao, J., Yang, Y., Li, M., Cao, J., et al. (2024). Risk factors for venous ulceration in patients with varicose veins of lower extremities. *Wound Repair and Regeneration, 32*(1), 47–54. https://doi.org/10.1111/wrr.13139
Bukayev, Y., Bukayeva, A., Muralev, Y., Nurbayeva, F., Uisimbayeva, Z., & Jumasheva, K. (2025). Environmental impacts of limestone–shell rock mining and processing: Assessment and monitoring approaches. *Acta Innovations, 57*(4), 1–19. https://www.actainnovations.com/index.php/pub/article/view/494

Hernández, R. M., Argandoña, R. G., Pintado, P. R. C., Baca, J. E. G., Castro, G. O., Barrientos, L. M. Z., … Trigozo, T. C. (2025). Strategic digital transformation in higher education and its effect on organizational agility and innovation performance. *Acta Innovations, 57*, 31–43. https://doi.org/10.62441/actainnovations.v57i3.513

Burian, E. A., Sabah, L., Karlsmark, T., Kirketerp-Møller, K., Moffatt, C. J., & Thyssen, J. P. (2022). Cytokines and venous leg ulcer healing: A systematic review. *International Journal of Molecular Sciences, 23*(12), 6526. https://pmc.ncbi.nlm.nih.gov/articles/PMC9224200/

Norman, G., Westby, M. J., Rithalia, A. D., Stubbs, N., Soares, M. O., & Dumville, J. C. (2018). Dressings and topical agents for treating venous leg ulcers. *Cochrane Database of Systematic Reviews*, 2018(6), CD012583. https://pmc.ncbi.nlm.nih.gov/articles/PMC6513558