

Venous Ulcers

Subjects: **Peripheral Vascular Disease**

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Venous leg ulcers (VLUs) are the most severe complication caused by the progression of chronic venous insufficiency. They account for approximately 70–90% of all chronic leg ulcers (CLUs). A total of 1% of the Western population will suffer at some time in their lives from a VLU. Furthermore, most CLUs are VLUs, defined as chronic leg wounds that show no tendency to heal after three months of appropriate treatment or are still not fully healed at 12 months. The essential feature of VLUs is their recurrence.

venous ulcer

recurrent venous ulcer

compression therapy

conservative treatment

invasive treatment

costs

prevention

1. Definition of Venous Leg Ulcer

According to the CEAP classification, revised in 2004, a venous leg ulcer (VLU) is defined as a full-thickness skin defect, most frequently in the lower leg and ankle region, that fails to heal spontaneously and is sustained by venous hypertension due to chronic venous disease ^[1]. Venous leg ulcers (VLUs) usually occur at the malleolar part on the medial and lateral sides of the ankle. However, they also may appear on the supra-malleolar and infra-malleolar areas of the leg and foot ^[2]. Furthermore, most VLUs are chronic leg ulcers (CLUs), defined as chronic leg wounds that show no tendency to heal after three months of appropriate treatment or are still not fully healed at 12 months ^[3]. Moreover, it is estimated that between 40% and 50% remain active between 6 and 12 months, and that 10% remain active up to 5 years ^[4]. It also has been shown that a VLU that fails to decrease in size by 30% (percentage area reduction) of its initial size over the first four weeks of treatment has a 68% probability of failing to heal within 24 weeks ^[5].

2. Pathophysiology of Venous Ulcers

Patients with venous leg ulcers have venous hypertension and abnormally sustained venous pressure elevation upon ambulation (normal venous pressure decreases with walking), which results from vein reflux or outflow obstruction.

Venous outflow may also be impaired due to poor calf muscle pump function, which damages the venous system's ability to overcome the venous blood return to the heart. The limitation of ankle movement seems to be an

essential contributor to calf muscle pump failure and a risk factor for ulceration [6]. Several risk factors of VLU development have been identified, including, among others, an age older than 55 years, an increased body mass index (BMI), a family history of CVI, a history of venous thromboembolism disease and superficial thrombophlebitis, a sedentary lifestyle, skeletal or joint disease of the legs, multiparous women, and severe stages of chronic venous diseases (lipodermatosclerosis, active or healed venous ulcers in history) [7].

Although venous hypertension results in ulceration, the exact mechanism remains unclear. Several hypotheses have been proposed, such as abnormalities of the fibrinolytic system, peripapillary fibrin deposition causing decreased oxygen diffusion to tissues, the trapping of growth factors by extravasated macromolecules around the vessels and in the dermis, limiting their function, and leucocyte margination and activation with the subsequent local release of inflammatory mediators [8]. Consequent microcirculatory changes lead to venous hypertensive microangiopathy (enlarged permeable capillaries, abnormally increased skin flux, edema, altered microlymphatic circulation, decreased partial pressure of oxygen, and increased carbon dioxide) that results in ulceration [9].

The effect on the microcirculation begins with altered shear stress on the endothelial cells, causing them to release vasoactive agents and express selectins, inflammatory molecules, chemokines, and prothrombotic precursors [10] [11]. Mechanical forces and low shear stress are sensed by the endothelial cells via intercellular adhesion molecules-1 (ICAM1, CD 54), vascular cell adhesion molecules1 (VCAM-1, CD-106), and endothelial leucocyte adhesion molecule1 (CD-62, E-selectin). CVD patients have increased expressions of ICAM-1 and VCAM-1. A key component of inflammation in VLUs is the increased expressions of matrix metalloproteinases and the production of cytokines (Transforming growth factor- β 1, Tumor necrosis factor- α , Interleukin-1) [12].

Another area of research in the pathophysiology of VLUs is gap junctions. Gap junctions are proteins that play critical roles in the pathogenesis of chronic wounds, mainly involved in inflammation, edema, and fibrosis. Connexins (a component of gap junctions) are abnormally elevated in the wound margins of VLUs. Connexins seem to play an essential role in the inflammatory response and VLU healing [13].

The pathophysiology of venous ulcers is shown in **Figure 1**.

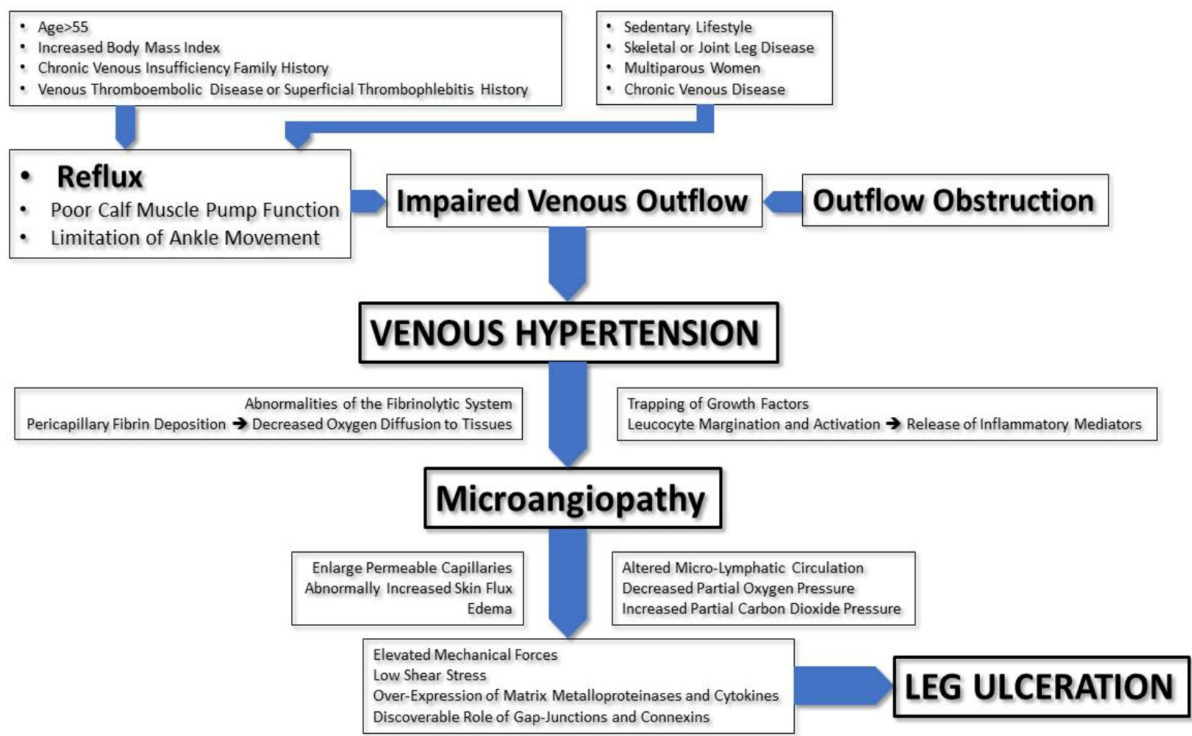


Figure 1. Pathophysiology of venous ulcers.

3. Diagnosis of Venous Ulcers

The diagnosis of leg ulcers is based on medical history, clinical assessments, functional/diagnostics testing, blood tests, biopsy, bacteriologic or mycologic swabs, histopathology, and direct immunofluorescence [\[14\]\[15\]\[16\]\[17\]](#) (Table 1). The clinical diagnosis as the first step is available everywhere, allowing for the diagnosis of the majority of VLUs. In the next step, several complementary diagnostic procedures are used [\[12\]\[14\]](#) (Table 2).

Table 1. Diagnostics of leg ulcers.

Medical History	
History of present symptoms and signs	Duration and presence of symptoms: Cramps, tired legs, swollen legs, heavy legs, restless legs, venous claudication, itching Pain: distribution, intensity (VAS score 0–10), duration, intermittent, during night/day, pain during dressing changes
	Duration and presence of signs: Varicose veins: duration, uni-/bilateral, bleeding from the vein Swelling: uni-/bilateral, region: around the ankle, whole leg, relation to standing/sitting a whole day Active ulcer: spontaneous/post-traumatic, duration, dressings (type/frequency of changes), compression therapy

Past signs	Previously healed/recurrent ulcers: spontaneous/post-traumatic, duration, dressings, compression therapy DVT/SVT/PE: time of occurrence, therapy Previous leg fractures Previous surgical therapy
Comorbidities	Diabetes mellitus, hypertension, chronic renal insufficiency, heart failures, malignancy, rheumatoid arthritis, PAD, obesity, back problems
Treatment	Treatment of present and past varicose veins: laser, sclerotherapy, surgical treatment, endovenous ablation (non-thermal/thermal), compression therapy (short-/long-stretch bandages, stockings, Velcro® materials) Treatment of present ulcer: dressings, therapy of surrounding skin, compression; where and by whom treatment is provided (patient/nurse/in hospital/in healthcare center); medications (anticoagulants, contraceptives, hormone replacement therapy, antidiabetics antihypertensives, immunosuppressive therapy, other)
Allergies	Contact/systemic drug reaction
Pregnancy	When, number, signs, and symptoms during pregnancy, therapy of signs/symptoms
Family history	Presence of varicose veins in relatives, ulcers, DVT
Occupation	Prolonged standing/sitting
Bad habits	Smoking, alcohol consumption, drug use
Trauma	Mechanical, chemical, radiotherapy, chemotherapy, etc.
Clinical Assessment	
Inspection and palpation	Mobility, BMI Presence of varicose veins, corona phlebectatica Limb swelling: Stemmer's sign, non-pitting/pitting, Bisgaard sign Skin changes: hyperpigmentations/redness (whole leg/during the vein, eczema), lipodermatosclerosis/atrophie blanche Peripheral arterial pulses, capillarity refilling Groin lymph nodes Leg temperature (cold/warm) Scars after previous surgical therapy, trauma Trophic changes in nails
	Leg ulcers: where, number, size, wound bed (necrosis, fibrin (ogen), granulation tissue, epithelial tissue, isles in wound bed), edges, surrounding skin, smell, presence of infection, wound exudate, possibility of ankle movements
Functional/Diagnostics Testing	

Venous system	CW Doppler: S–F junction reflux Duplex US Photoplethysmography	
Arterial system	Measurement of ABI (with CW Doppler; automatic)	
Lymphatic system	Limb circumferences, perimetry, bioimpedance	
Non-invasive/invasive tests	Monofilament test Capillaroscopy Venography IVUS Angiography Lymphoscintigraphy CT MR	
Microbiological	Swab for pathogenic bacteria and fungi	
Skin/ulcer biopsy	Pathohistological examination Direct immunofluorescence	
	Complete/differential blood count, C-reactive protein, erythrocyte sedimentation rate, blood glucose, HBA1c, blood lipids electrolytes, urea, creatinine, liver function tests tests of coagulations	
The Questions We Ask Ourselves	The Causes/Symptoms/Signs	Tests for Making the Diagnosis
What is the immediate cause of the wound?	<ul style="list-style-type: none"> - Trauma - Too-tight compression - Spontaneous 	
Is there any underlying pathology?	<ul style="list-style-type: none"> - Venous disease: vein symptoms: varicose veins; mild ankle swelling during the day; hyperpigmentation; corona phlebectatica; lipodermatosclerosis; stasis eczema; atrophie blanche; past DVT/SVT; varicose veins/ulcer in family; reflux at SF junctions; insufficient veins at DU investigations; venography - Arterial disease: intermittent claudication; rest pain; poor perfusion (loss of pedal pulses, cold foot, pale skin); atrophic skin; loss of hair on the leg; trophic changes or gangrene; necrosis on the wound bed 	<ul style="list-style-type: none"> - Reflux at SF junctions, insufficient veins at DU investigations, plethysmography, venography - Blood lipids, low ABI (below 0.85 or below 0.5), arteriography - Blood glucose, HBA1c, monofilament test,

The Questions We Ask Ourselves	The Causes/Symptoms/Signs	Tests for Making the Diagnosis	
	<ul style="list-style-type: none"> - Mixed venous–arterial etiology - Diabetic leg ulcer: neuropathic: warm, sensory deficit, diminished sweating, dry skin, motor neuropathy with a high arch and claw toes, Charcot foot; ischemic: pale, cold, absence of pulses, intermittent claudication; neuro-ischemic foot - Vasculitis: pain ulcers; small ulcers with necrosis - Malignancy: usually no pain; hypertrophic ulcers - Infection: high body temperature, redness around the ulcer - Bullous dermatosis - Lymphoedema stage III: primary or secondary cause lymphoedema: papillomatosis, Stemmer’s sign, non-pitting/pitting edema 	<ul style="list-style-type: none"> - capillaroscopy, ABI - ANCA, biopsy (HPE, DIF) - Biopsy - Swab, CRP, ESR, complete/differential blood count - Pemphigus and pemphigoid antibodies, biopsy - Limb circumferences, perimetry, bioimpedance, lymphoscintigraphy 	
Does the patient have any (medical) conditions? [15] [17]	Diabetes mellitus, malnutrition, cardiovascular disease, anemia, renal disease, rheumatoid arthritis, cerebrovascular disease, old age, reduction in sensory perception, increasing susceptibility to trauma, therapy with immunosuppression agents, malignancies and their treatment, smoking, alcohol consumption, drug use, prolonged standing/sitting, obesity, poor mobility		differential can differ

Regarding investigations, individual studies’ recommendations could be more robust [\[10\]](#)[\[11\]](#) (Table 3).

Table 3. Recommendations of investigations in patients with venous leg ulcers/level of evidence. SF—saphenofemoral; DU—Doppler ultrasound; DVT/SVT—deep-vein thrombosis/superficial-vein thrombosis;

Palpation of lower-extremity arterial pulses and calculated ABI are recommended for all patients with suspected venous leg ulcers	C	toplasmic C-reactive
Duplex ultrasound sonography is recommended for patients with venous leg ulcers to assess venous reflux and/or obstruction	C	
Biopsy is recommended for patients with venous leg ulcers if healing stalls	C	
Biopsy is recommended for patients with ulcers if there is suspicion that the ulcer may be venous, but it has an atypical appearance	C	

Referral to a subspecialist is recommended for patients with venous leg ulcers if healing stalls	C	
Referral to a subspecialist is recommended for patients with ulcers if there is suspicion that the ulcer is not venous, but it is of an atypical appearance	C	
Screening of patients using a hand-held Doppler detector makes sense only in mild involvement when only telangiectasias and venectasias are present	C	
X-ray contrast venography, magnetic resonance, or computed tomography venography are reasonable to perform only in a small number of selected patients who have anatomical venous anomalies, and in those patients in whom surgical intervention on the deep venous system is planned.	C	ients with mbosis, in

diseases of the skeleton or joints of the lower extremities (due to poor mobility or immobility of the ankle), in women with multiple pregnancies, or in those on therapy with oral contraceptives. On the basis of the epidemiological data previously mentioned, patients who have lipodermatosclerosis and other signs of venous disease or venous insufficiency, and in patients who have typical evening swelling of the legs. Poor prognostic signs for healing are an ulcer duration longer than three months, an initial ulcer size of 10 cm or more at the start of treatment, and the presence of lower-extremity arterial disease. Patients with venous ulcers have ulcers that are usually shallow with well-defined edges and that are often located in the lower two-thirds of the lower leg. Signs of venous disease, such as varicose veins, edema, corona phlebectatica, atrophie blanche, and eczema due to stasis, may also be present. At the same time, patients should have palpable pedal pulses and a calculated brachial–ankle index above 0.85. On Duplex ultrasound, superficial and/or deep veins or perforating veins are insufficient. Severe complications include infection and malignant changes in the ulcer. All these symptoms and signs, as well as associated diseases and specifics in the anamnesis and clinical picture, as well as objections to investigations, help us diagnose venous ulcers and distinguish them from other possible causes of leg ulcers [18][19][20].

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