

## ORIGINAL ARTICLE

# Chronic venous insufficiency and venous leg ulcers: Aetiology, on the pathophysiology-based treatment

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## Abstract

The chronic venous disease covers a wide spectrum of venous disorders that are characterized by severely impaired blood return that primarily affects veins in the lower extremities. Morphological and functional abnormalities of the venous system led to chronic venous insufficiency (CVI), and present as leg heaviness/achiness, edema, telangiectasia, and varices. The term ‘chronic venous insufficiency’ (CVI) refers to a disease of greater severity. Venous dysfunction is associated with venous hypertension and is associated with venous reflux due to poorly functioning or incompetent venous valves, which ultimately reduces venous return, leading to a cascade of morphological, physiological, and histologic abnormalities such as blood pooling, hypoxia, inflammation, swelling, skin changes (lipodermatosclerosis), and in severe cases, venous leg ulcers (VLU). This review summarizes recent knowledge about the aetiology, risk factors, and pathophysiology of VLU and compared the possibilities of their treatment.

## KEYWORDS

chronic venous insufficiency, compression therapy, therapy, venous leg ulcers, wound coverage

## Key Messages

- Chronic VLU as a most probable result of CVI is associated with pain and a poor prognosis.
- Recognizing the molecular processes behind VLU has resulted in developing novel approaches to treatment.
- All risk factors for the recurrence of VLUs should be identified and summarized to provide recommendations to guide preventive strategies for recurrence.

## 1 | INTRODUCTION

Chronic venous insufficiency (CVI) is a common pathology affecting thousands of individuals worldwide. According to

the Clinical, Etiological, Anatomical, and Pathophysiological classification, reliable and reproducible grading of the severity of venous insufficiency enables one to choose the proper therapy.<sup>1</sup> The development of CVI likely has several

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TABLE 1 Risk factors for chronic venous disease.

Non-modifiable	Modifiable
Genetic predisposition	Obesity (BMI > 30 kg m <sup>-2</sup> )
Age	Prolonged sitting or standing
Female gender	Physical inactivity
Family history of venous disease	Hormonal factors (pregnancy, use of oral contraceptives or oestrogen substitution treatment)
Trauma or leg injury/fracture	Smoking

contributory factors, including a hereditary component and many risk factors (Table 1).<sup>2–5</sup> Venous dysfunction originates from venous hypertension and is associated with venous reflux due to poorly functioning or incompetent venous valves, which ultimately reduces venous return, leading to blood pooling, hypoxia, and inflammation.<sup>6</sup> Valvular injury in the vein or vein occlusion occurs as well. Venous dysfunction causes high blood pressure within the veins, venous hypervolemia, swelling, lipodermatosclerosis, and, in severe cases, venous ulcers. CVI is widely associated with severe types of venous-related complications, notably venous leg ulcers (VLU). VLU are more prevalent with higher age, which negatively affects their healing and recurrence. The majority (up to 80%) of patients develop a recurrence within 3 months.<sup>7</sup>

Genetic predisposition due to polymorphism of forkhead box protein C2 gene (FOXC), hemochromatosis gene (HFE), and genes of matrix metalloproteinases (MMPs) has been also described in the development of CVI.<sup>8</sup> However, polymorphisms in these candidate genes are rare and only affect predisposition to the disease. MMPs polymorphisms have been shown to be a good tool to better identify patients at higher risk of CVI, which may influence the selection of appropriate prevention and treatment strategies aimed at slowing disease progression and complications of CVI.<sup>8</sup> Activated MMPs change the structural components of the vein wall collagen and elastin, resulting in extracellular matrix degradation. Therefore, overexpression of MMPs (together with cytokines) might be responsible for VLU formation.<sup>9</sup> MMPs were detected in high quantities in VLU and in the wound fluid, and the correlation of increased expression of MMPs is associated with poor healing.<sup>10</sup>

## 1.1 | CVI is a major cause of VLU

CVI is characterized by persistent regressive venous pressure, which causes the capillaries to dilate and

venous blood deposits in the skin microvasculature. The deposition of blood causes fluid overload (hypervolemia) in the veins and subsequent peripheral edema. This condition disrupts the healthy, uninterrupted interchange of blood in the capillaries from the arteries and the veins. Aggregated venous blood in the veins is deoxygenated, accumulates under the skin, and causes ‘venous ischemia and hypoxia’. The extreme signs of the disease include inflammation, skin changes, and then VLU,<sup>1</sup> which are usually related to the poor well-being of patients. It was already shown that in young patients with venous reflux, the venous system appears to present an enhanced dynamism and arterialization of the venous wall, which may be a reason for the premature aging and a pathological environment of the tissue.<sup>11</sup>

Aside from its substantial predominance, CVI has a considerable negative influence on living standards. CVI affects the functional capacity of patients, even in those with a milder form of the disease. CVI was found to be more prevalent in obese people in industrial countries and after long-term standing posture. Taengsakul (2022) has shown that in the Tai population, the BMI of patients with severe CVI was significantly higher compared to patients suffering from mild-to-moderate CVI.<sup>4</sup> The severity of CVI increases with age, affecting the female population more often.<sup>2</sup> Severe symptoms can result in reduced mobility.<sup>5</sup> Also, these authors have shown that the majority of patients who perform regular physical activity had less severe CVI. Nevertheless, almost all individuals suffer from symptoms of CVI, such as pain, burning, leg heaviness, dry skin with itchiness, and skin damage with sore ulcer growth in the malleoli region.

Both reflux and obstruction account for the pathophysiology of CVI. Several metabolic and genetic factors were described to affect predisposition to CVI, and thus also to venous ulceration. Various metabolic factors are considered as the risk factors for CVI, for example, low serum magnesium levels may pose a potential risk for the development of CVI.<sup>12</sup> Micro- and macro-vascular complications belong to chronic complications of diabetes mellitus (DM).<sup>13</sup> However, the potential association between DM and CVI has not been fully elucidated yet. CVI and mostly type 2 DM are linked by the same common risk factors: obesity, a sedentary lifestyle, lack of physical activity, polygenic inheritance, higher age, prothrombotic state, and, therefore, higher probability of thromboembolic disease and hormone therapy. An important factor accompanying CVI is the venous circulation's inflammation that leads to increased inflammation within the vein wall and extravasation of inflammatory cells and molecules into the interstitium (for review see Raffetto, 2018). The characteristic appearance of lipodermatosclerosis results from the breakdown of red blood cells and the subsequent

deposition of hemosiderin in the skin.<sup>1,14</sup> Lower extremity edema is common in CVI.

The extravasation of 2-macroglobulins, fibrinogens, as well as other biomolecules from veins to the dermis, is thought as a causative factor responsible for capillary dilation or damage to endothelium cells as a consequence of high blood pressure in the veins.<sup>15</sup> Altered microcirculation is important in the development of CVI and it begins with altered shear stress on the endothelial cells that release vasoactive agents, express selectins, inflammatory molecules, chemokines, and prothrombotic precursors.<sup>10</sup> Endothelial to mesenchymal transition in human varicose veins was demonstrated due to altered shear stress, probably via activation of BMP4/pSMAD5-SNAI1/2 signalling.<sup>16</sup> These biomolecules have the potential to interfere with the ability of spontaneous signalling pathways to preserve tissue structure and promote regeneration and recovery. One of the commonly detected biomolecules is transforming growth factor  $\beta$  (TGF $\beta$ ), which is considered a growth inhibitory cytokine. In nonhealing venous ulcers, TGF $\beta$  signalling is attenuated by lower expression of its receptors, which diminished activation of the Smad signalling cascade. Subsequent deregulation of TGF $\beta$  target genes leads to loss of tissue homeostasis and hyperproliferation.<sup>17</sup> This factor and some others promote angiogenesis and collagen synthesis (for review see Krizanova et al., 2022).<sup>18</sup>

Venous reflux can trigger the production of reactive oxygen species (ROS). Ortega et al. (2019) have shown that young patients with venous reflux demonstrate higher levels of lipid peroxidation and oxidative stress, which reflects the characteristics of an aged patient.<sup>19</sup> Also, the overproduction of ROS drives persistent local inflammation and the development of lipodermatosclerosis.<sup>20</sup> Therefore, strategies oriented towards the use of antioxidants can be beneficial tools in the treatment of CVI. Varicose veins are characterized by chronic oxidative stress and significantly decreased antioxidant defence in comparison to a normal vein, which consequently leads to inflammation. Flavonoids as potent antioxidant compounds can reduce the risk of atherosclerosis development, prevent thrombotic incidents, and they can inhibit inflammation.<sup>21</sup> Some of the bioflavonoids, such as rutin or aescin are already used as vasoprotective compounds, aimed to present anti-inflammatory properties and improve CVI signs and symptoms.<sup>6</sup> Recently, a novel compound containing troxerutin, diosmin, horse chestnut, and vitamin C might be of interest to counteract the harmful CVI-associated vascular effects.<sup>22</sup>

## 1.2 | Venous leg ulcers (VLU)

VLU are chronic wounds defined as skin defects, located mainly in the distal shank.<sup>23</sup> Skin damage develops due to

venous hypertension and limb edema and is characterized by symptoms of pain, limb heaviness, and lifestyle-limiting ambulation. Associated signs include varicose veins, dermal weeping, stasis dermatitis, skin hyperpigmentation, and subcutaneous fibrosis.<sup>23</sup> VLU are a serious medical challenge and the result of CVI, initiated by elevated venous pressure that can be caused due to venous occlusion and/or varicose veins.<sup>24,25</sup> Healing time ranges from a few months to several years and approximately, 25% of VLU did not heal.<sup>26</sup> VLU are the most common chronic leg ulcers in the geriatric population, especially among persons with DM, mainly due to age-increased neuropathy and localized ischemia.<sup>27</sup> Other risk factors associated with VLUs include being overweight, a record of a prior injury, inactivity, and hereditary thrombophilic disorders like the factor V Leiden variant.<sup>28</sup> Chronic VLU can also be caused by vascular dysfunction, rheumatoid arthritis, injury, sickle cell disease, vasculitis, and epidermal tumours, and their treatment is worsened by age.<sup>7</sup> Stasis (venous) dermatitis represents a cutaneous manifestation of venous hypertension and is an indication of underlying vascular pathology and, if undiagnosed or left untreated, is a precursor to venous ulcers.<sup>29</sup>

VLUs present as exposed skin lesions that arise in venous hypertension-affected areas of the lower limbs.<sup>30</sup> The pathogenesis of venous ulcers is a complicated procedure that includes symptoms like varicose veins, persistent secretion, pruritus, skin discoloration, and scarring. Clinically, these defects can vary in size from small 'spots' to large circular defects affecting up to several percent of the body surface (TBSA-Total Body Surface Area). Similarly, they vary in depth from superficial defects to deep crater-like tissue involvement down to the muscle fascia. Macroscopically, these non-healing wounds can also vary in appearance from clear pink granulation to plaque to firmly adherent necrosis. The ulcers often have an unusual structure with firmly marked boundaries and are usually seen in the perimalleolar site, respectively, distal third of shank.<sup>23</sup> Even though most ulcers are only a few layers, profound infection may result in case of substantial tissue damage.

A few cases, meanwhile, are induced by unilateral varicose veins existing in the inferior saphenous vein.<sup>31</sup> CVI is diagnosed using medical criteria, such as skin conditions produced by persistent venous high blood pressure, physiological skin abnormalities including discoloration induced by hemosiderin accumulation, white atrophy, lichenification or dermatoliposclerosis, and stasis dermatitis. Testing methods are usually utilized to diagnose venous pressure and rule out other diseases that may be present. VLUs can appear as singular or several ulcers that have minimal depth, unevenly curved sides with proper edges, and exudes a yellowish-white liquid. The lesions

also have granulation and fibrous tissue, whereas necrotic tissue is uncommon. The pain caused by ulcers can be minimal, moderate, or severe. Lesions can also cause edema of the lower extremities, eczema and/or itching, lipodermatosclerosis, or hemosiderin accumulation; and cause the surface-level veins to dilate and convolute.

VLU is a serious medical concern. Achieving a quick healing process without a relapse after the intervention is crucial.

### 1.3 | Possibility of treatments for venous leg ulcer

Possibilities to treat venous ulcers include mechanical modalities, pharmacologic treatment, advanced wound therapy, and surgical options. Treatment of VLU depends on several factors, like age, diabetic status, malnutrition, ulcer localization, etc.<sup>27</sup> Treatment of VLU should include cleaning of affected tissue, removal of debridement, prevention of infection, and promotion of healing.<sup>32</sup> The most common VLU treatment includes compression therapy and exercise. Wound drainage, pain, application, and physical impairment can form barriers to compression therapy.<sup>33</sup> Also, arterial insufficiency and uncompensated congestive heart failure are contraindicatory to compression therapy. Pressure marks, pain, necrosis, friction damage, and leg ulcer formation, as a result of poorly applied compression or the improper type of compression, skin damage, etc., were identified as risk factors and adverse events.<sup>34</sup> Pharmacologic treatment is based on knowledge about affected/altered metabolic pathways due to ulcer formation. Some signalling pathways involved in cutaneous wound healing, for example, calcium signalling, ROS, and gasotransmitters were already described in our review.<sup>18</sup>

#### 1.3.1 | Compression therapy

Compression therapy is the basis of VLU treatment. Generally, tension prescription depends on the disease severity and is in the range of 20–50 mmHg.<sup>1</sup> A higher compression pressure (over 45 mmHg) resulted in a higher proportion of healed VLU during a period of 24 weeks.<sup>35</sup> Also, it was demonstrated that the effectiveness of compression therapy might affect the recurrence of VLU. Milic and coworkers published an open, prospective, randomized, single-centre study that included 477 patients (240 men, 237 women; mean age 59 years).<sup>36</sup> After the randomization of patients, they were allocated to wear elastic stockings with different pressure: 18–25, 25–35, and 35–50 mmHg. Within the period of 10 years,

recurrence of VLU occurred in 96% of individuals allocated to wear stockings with 18–25 mmHg pressure, 66.9% of those wearing stockings with 25–35 mmHg pressure, and 24.5% treated with multilayer compression system exerting 35–50 mmHg). Thus, the force of the compression can not only affect the healing but also the recurrence of VLU.

#### 1.3.2 | Exercise

The exercise was shown to have a significant effect on VLU healing, particularly when combined with compression therapy.<sup>27,37</sup> Patients receiving both compression therapy and progressive tailored exercise training have a higher quality of life.<sup>38</sup> Tew and co-workers (2018) described that cutaneous microvascular reactivity may facilitate the healing of VLU.<sup>39</sup> They have shown that a 12-week supervised exercise program improved measures of cutaneous microvascular reactivity in people being treated with compression therapy for venous ulceration. Mutlak and co-workers (2018) have shown that VLU healing as the size of the ulcer was seen to have decreased significantly in the patients who had performed regular exercise.<sup>37</sup> It appears that the combination of progressive resistance exercises and aerobic activity (e.g. walking) may be the most effective form of exercise regimen.<sup>40</sup> Different forms of exercise and optimal exercise doses (including progressive resistance exercise, walking, and ankle exercises) are being compared.<sup>41</sup> Resistance exercise training, defined as an exercise strategy whereby muscles contract against an external resistance, revealed an approximately 70% reduction in ulcer area after exercise after 12 weeks of training, probably due to better skin oxygenation.<sup>42</sup>

#### 1.3.3 | Pharmacologic intervention—phlebotonics

Phlebotonics represent a heterogeneous group of compounds—mostly plant flavonoids, classified as venoactive and vasoprotective agents. Moreover, there are many differing opinions in the literature on the use of phlebotonics, ranging from a beneficial effect in CVI to serious side effects. Micronized Purified Flavonoid Fraction (diosmin) was found to have beneficial effects without serious adverse events<sup>43</sup> and was suitable for reduction in symptoms of chronic venous disease, such as edema. Phlebotonics were reported to slightly reduce edema and also ankle circumference.<sup>44,45</sup> Flavonoids are rather classified as ‘medical food’<sup>43</sup> and are suggested for venoprotection instead of the VLU treatment.

Pentoxifylline is a xanthine derivative with a variety of beneficial anti-inflammatory and hemorrheological properties. Pentoxifylline was shown to have a clear benefit in healing VLU,<sup>46</sup> either alone or in combination with compression therapy.<sup>47</sup>

### 1.3.4 | Pharmacologic intervention—antibiotics and antimicrobial effect

Since VLU forms open wounds, proper antibiotic/antimicrobial coverage can be used to prevent microbial adherence, colonization, and infection. Microbiological research revealed that leg ulcers can be colonized by both Gram-positive and Gram-negative bacteria. The most prevalent Gram-negative bacteria isolated in leg ulcer infections are *Pseudomonas aeruginosa* and *Escherichia coli*, while *Staphylococcus aureus* predominates among the Gram-positive microorganisms.<sup>48</sup> Infection is more likely in older people with large VLU. To prevent bacterial resistance, most guidelines recommend the use of antimicrobial dressings, antiseptics, and antibiotics only for patients with infected wounds. Antimicrobial biomaterials can serve as a perfect balance between promoting healing and preventing infection, thus they present a potential substitute for systemic treatment of chronic wound infections.<sup>49</sup> Because of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not for bacterial colonization.<sup>50</sup> Further, anti-inflammatory agents (e.g., statins) are a good choice.<sup>33</sup>

### 1.3.5 | Wound coverage: skin grafts and dressings

Recently, the development of various biomaterials for wound care, including bioengineered skin grown from human donor cells (allografts), preserved skin from other animals (xenografts), etc., opened a new field in VLU treatment. Over 100 skin substitutes are commercially available.<sup>51</sup> However, the use of these materials in medical practice is not yet sufficiently studied. In surgical therapy, skin transplantation with meshed Split-thickness skin grafts (STSG) is usually used after the preparation of the wound bed by conservative methods or NPWT (negative pressure wound therapy). Skin grafts are harvested with an electro- or air-dermatome, for example, from the anterior thighs, and meshed in a ratio of 1:1.5, 1:2, or 1:3 depending on the area of the defects. Prior to reconstruction, efforts are made to eliminate mostly polymicrobial colonization of the wound bed as much as possible. In

practice, however, we very often encounter failure of skin graft adherence or with graft healing early after transplantation.<sup>52</sup> Covering venous ulcers by dressing is beneficial since ulcers promote moist wound healing. Recently, several compounds, which can increase the rate of healing of chronic wounds can be crosslinked to the dressing matrix. Different types of dressing can be used: hydrocolloids, collagen gels, hydrogels, or transparent film, to hold the moisture on the wound bed to prevent desiccation.<sup>53</sup> Recently, the use of innovative robotic wound systems, which have a number of advantages, especially with regard to high exudation of typically viscous wound fluids and the possibility of sustained compression of the dressing, has been intensively developed.<sup>54</sup>

### 1.3.6 | Other types of treatment

Other types of treatments were tested in VLU healing. Hyperbaric Oxygen Therapy is predominantly used to treat diabetic wounds. However, this therapy does not significantly affect the healing of VLU.<sup>55</sup>

Sclerotherapy and venous ablation are two forms of percutaneous treatment for CVI. Endovenous excision is the administration of heat energy to the vascular wall, generally endovenous laser treatment (EVLT) or radiofrequency (RF), which causes clotting usually accompanied by fibrotic scarring of the targeted section. Both RF and laser methods for great saphenous vein (GSV) ablation entail ultrasonic implantation involving GSV, followed by the introduction of a catheter to the region of the sapheno-femoral confluence. In a study, where 217 patients underwent RF ablation, the occlusion rate of saphenous veins was 100% at 3 years and 95.4% at 5 years.<sup>56</sup> Laser therapy has achieved occlusion levels of as much as 95% in 2 years without any severe problems. Venous ablation by either EVLT or RF seems to have a greater chance of success than sclerotherapy and a reduced risk of comorbidities than common surgical closure and removal.<sup>57</sup>

Another approach includes the cold atmospheric pressure plasma (CAP).<sup>58</sup> The disinfectant effect of CAP therapy appears to be the most well-established characteristic, as evidenced in multiple in vitro and in vivo experiments, as described previously. Furthermore, the prevention of microbial growth is a crucial priority in current tissue-repairing techniques since microbial proliferation hinders tissue-repairing and promotes chronic conditions.<sup>59</sup> The repetitive application of CAP can improve microcirculation and boost oxygen saturation in chronic wounds.<sup>60</sup> Another effect of plasma therapy is the activation of transcription factors for angiogenesis, which also serves as a key process in tissue regeneration. Furthermore, researchers have discovered in earlier investigations that plasma therapy lowers pH, which

causes lesion acidification. Wound acidification is a biological process that happens during the recovery period which could be advantageous in the therapy of a prolonged tissue repair.<sup>61</sup> Therefore, acidic buffers were tested to boost healing of VLU. Repetitive CAP application boosts and prolongs tissue oxygen saturation and capillary blood in chronic wounds, which can result in wound healing-promoting effects.<sup>60</sup> However, further experiments are required to clarify this issue.

For the past three decades, homologous platelet-rich plasma (PRP) was employed in a range of surgical settings, involving bleeding minimization<sup>62</sup> and cell renewal acceleration.<sup>63</sup> The application of PRP in the treatment of VLU has been described in a few research studies<sup>64–66</sup>; however, there is a dearth of convincing data from better randomized control trials. To activate tissue repair processes, electromagnetic stimulation<sup>67</sup> and ultrasonic therapies<sup>68</sup> have been utilized.

Negative pressure machines are utilized to remove liquids and particles from a specific area.<sup>69</sup> Up to now, negative pressure wound therapy (NPWT) is very limited in the treatment of VLU. NPWT affects only the wound surface, not the obstruction or venous reflux in the deep or superficial system. The benefit of NPWT increases with wound size. NPWT is suggested to treat ulcers larger than 12 cm<sup>2</sup>. This treatment should be accompanied by compression therapy.<sup>70</sup> Despite the limited quality of the data, such supplemental therapies may enhance venous leg ulcer recovery with relatively lower relapses. Other combination therapy, including instructional (Smith et al. 2018) and mental therapies<sup>59</sup> may boost lesion recovery efficiency, although the data on their impact on the recovery period and VLU relapse is mixed.

Fibrin sealants are also a suitable option for VLU management. The fibrin sealant is vital in blood clotting and tissue recovery because the fibrous connectivity and peptide structure linked with it not only stimulate neovascularization, collagen formation, and ulcers constriction but also lead to rapid re-epithelization (for review see<sup>71</sup>). Fibrin sealant is a great barrier to integrating and encouraging cellular proliferation and the production of signalling pathways and antibiotics since it remains in the lesion bed for a minimum of 4 days and completely degrades within 10 days.<sup>72</sup> Three basic forms of fibrin sealants are present up to now: (i) autologous (derived from a person's own coagulation and cryoprecipitate); (ii) homologous (coagulation and cryoprecipitate from a 'pool' of blood serum contributors); as well as (iii) heterologous (derived from animal components). Because the quantity of autologous fibrin sealant derived from the person's own coagulation and cryoprecipitate is little, its application is impractical.

Furthermore, regardless of steps made by producers to limit the danger of virus infection, homologous fibrin sealants may facilitate the transfer of contagious or pathogenic disorders.<sup>73</sup> Recently, heterologous fibrin sealants (HSF) were developed. They consist of a fibrinogen-rich cryoprecipitate extracted from *Bubalus bubalis* buffalo blood and a thrombin-like enzyme purified from *Crotalus durissus terrificus* snake.<sup>74</sup> Stage I/II organized, single-arm medical research was recently conducted on thirty-one people, including 69 current chronic venous ulcers. For 3 months, all lesions were medicated with HFS. The following results were evaluated: a) initial tolerability, immunological testing, and validation of the minimum dosing regimen; and (ii) subsequent potential effectiveness by examining the recovery phase. There were no serious widespread negative effects associated with the usage of HFS. The following local side effects may be caused by therapies: lesion soreness (52%), peri-ulcer irritation (12%), peri-ulcer maceration (16%), severe infection (8%), peri-ulcer dermatitis (4%), the emergence of new blisters (4%), and an expansion in the affected region by lesions (4%). Based on the procedure and dosage suggested, the HFS supplement showed to be nontoxic and non-immunogenic, with excellent early effectiveness for the cure of LVU.<sup>74</sup>

The enhanced stromal vascular fraction (e-SVF) was utilized during a trial. The reporting of practical instances demonstrated that the use of e-SVF could promote cellular recovery.<sup>75</sup> Improved cellular longevity was achieved by enhanced vascularization and transcription factor release. The capability of cells found inside the e-SVF colony might reflect the possible advantage of e-SVF augmentation.<sup>76</sup> In the case of post-traumatic lower extremity ulcer, the cells in e-SVF produce numerous proliferation variables that enhance survivability and boost vascular permeability, resulting in improved graft function.<sup>77</sup> e-SVF could promote neo-angiogenic vasculogenesis as well as fibrotic function in fibroblasts, which promotes fat cell preservation and 3D structure.<sup>78</sup> In contrast to conventional fat transplantation, the graft's survivability seems to be more likely, and fat apoptosis may be minimized because of enhanced vascular growth in the transplanted location.

## 2 | CONCLUSION

Chronic VLU as a most probable result of CVI is associated with pain and a poor prognosis. The occurrence of VLU prevents a full life in both the physical and social spheres, significantly reducing the quality of life. Age, gender, BMI, and socioeconomic conditions are important risk factors not only for VLU occurrence but also for

the probability of recurrence. Various variables contribute to persistent venous ulcers; therefore, a multidisciplinary effort to thorough patient evaluation is essential to determine the pathophysiology, precise diagnosis, and appropriate management. Venous ulcers most commonly occur along the medial surface above the malleolus. Various concepts have been suggested to understand the pathophysiology of venous high blood pressure resulting in ulcers. Chronic conditions can affect venous disease therapy and necessitate simultaneous treatment. Although several different treatment approaches were determined up to now, compression treatment and exercise belong to the most effective approaches. Recognizing the molecular processes behind VLU has resulted in developing novel approaches to treatment. Biologic agents like fibroblast variants, bilayer living skin construct, and ECMs are becoming popular, in addition to poly-*N*-acetyl glucosamine, and amnion/chorion transplants. Often, a combination approach becomes beneficial.

Further knowledge is required to understand the recurrence of VLU. Recurrence is very often and can occur very early, especially when compression treatment of the VLU is lacking or is not proper. Pathophysiological risk factors associated with recurrence include a history of deep vein thrombosis, a history of multiple leg ulcers, and an increased duration of previous ulcer healing. Therefore, all risk factors for the recurrence of VLUs should be identified and summarized to provide recommendations to guide preventive strategies for recurrence.

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Olga Krizanova, Adela Penesova, Alica Hokynkova, Andrea Pokorna, Amir Samadian, and Petr Babula have no conflict of interest.

### DATA AVAILABILITY STATEMENT

No data was used for the research described in the article.

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