Chapter

Chronic Venous Ulcer

Walid A.M. Ganod

Abstract

This chapter sheds light on the cause and effect of chronic venous ulcers (CVUs) and the therapeutic procedures used to treat them. In the last two decades, many changes have occurred in the strategy of wound management through the development of adjunctive therapy that supports wound healing. Eventually, the latest development in platelet concentration technology produced platelet-rich fibrin (PRF). It was categorized as the second-generation platelet concentration family after platelet-rich plasma (PRP). Venous leg ulcers (VLUs) account for 70% of all leg ulcers and are estimated to affect 1% of the population; prevalence increases with age. The chronicity and refractory nature of venous ulcers have a great effect on the quality of life (QoL) and work productivity of patients, in addition to the expenditure of significant medical resources and efforts. Therefore, the goal of VLU management is to induce rapid healing without recurrence, which mainly helps to improve QoL. The first therapeutic procedure used in the treatment of VLU was compression therapy, in which the application of effective graduated compression decreased the overload in the venous system and venous reflux. Furthermore, it accelerated the capillary blood flow and decreased capillary fluid leakage, which alleviated limb edema.

Keywords: venous ulcer, ambulatory venous hypertension, chronic venous insufficiency, compression therapy, platelet-rich fibrin

1. Introduction

Chronic leg ulcers (CLUs) are chronic wounds that do not show a tendency to heal within a reasonable period. This period can determine the state of a chronic wound; if there is no tendency to heal after 3 months or if the wound does not fully heal after 12 months, the ulcer is determined to be chronic [1]. The aforementioned period is not a fixed number; it is governed by other factors, such as ulcer ethology, size, and so on [2].

In general, ulcers can be described in many ways; for instance, ulcers have a full-thickness wound, lack a source of re-epithelization in the center, and show poor tendency to heal.

The most common clinical cause of CLUs is venous insufficiency followed by arterial insufficiency, diabetes, or a combination of two or more of these factors [3].

The Wound Healing Society described chronic wounds as "a silent epidemic disorder" correlated to the percentage of the public with this condition. In the United States, approximately 6.5 million patients suffer from chronic nonhealed wounds. Therefore, two million working days are lost annually. In addition, in the United Kingdom, the annual incidence of leg ulcers has been estimated to be 3.5 per 1000 individuals [4].

Venous insufficiency is considered the most common cause of leg ulcers, accounting for 70% of leg ulcers. Inline arterial diseases and mixed venous and arterial disorders account for 10 and 15% of ulcers, respectively. There is a major challenge in the assessment and diagnosis of CLU in regard to miscellaneous disorders such as vasculitis and hematological diseases. These kinds of disorders represent the remaining 5% of the causes of CLUs [5].

Scottish guidelines define a chronic venous leg ulcer as "an open lesion between the knee and the ankle joint that remains unhealed for at least 4 weeks and occurs in the presence of venous disease" [6].

2. Anatomy of venous system in lower limbs

The anatomical variation and nonuniform nomenclature of the lower limb vein system, especially in the literature, supported the constitution of the International Interdisciplinary Committee in 2001 to perform adjustment and uniformity of the anatomical terminology of lower limb veins (**Figure 1**) [8].

The veins of the lower limb can be classified into three systems: superficial, deep, and perforator veins (**Figure 2**). These veins are arranged into two main compartments: superficial and deep compartments. A superficial compartment is present between the skin and muscular fascia, which contain superficial veins. A deep compartment that contains deep veins is present under the deep fascia. The perforator veins are connected to the superficial and deep system [9]. **Figure 3** shows that there is another compartment within the superficial compartment enclosing the saphenous vein, which is called the saphenous compartment.

The principle method for venous return from the lower limb is through the deep vein system, which pairs below the knee and accompanies arteries and then joins to form the popliteal vein that completely ascends as the femoral vein. The main veins in the superficial system that are the target of many venous therapies are the great saphenous vein and small saphenous veins, which are connected with communicator veins [10].

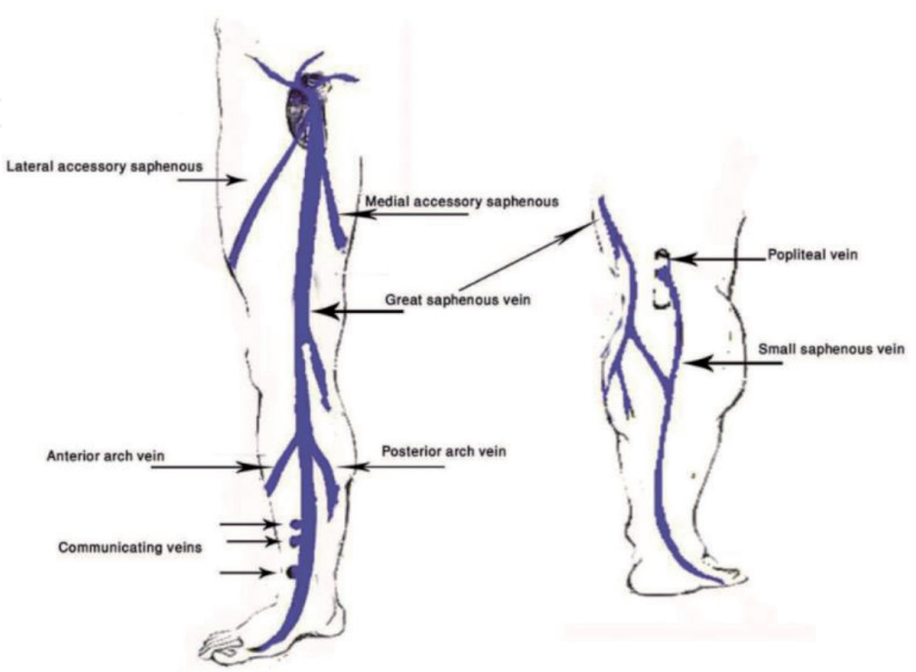

Figure 1.
Diagram of the superficial venous system of lower limbs [7].

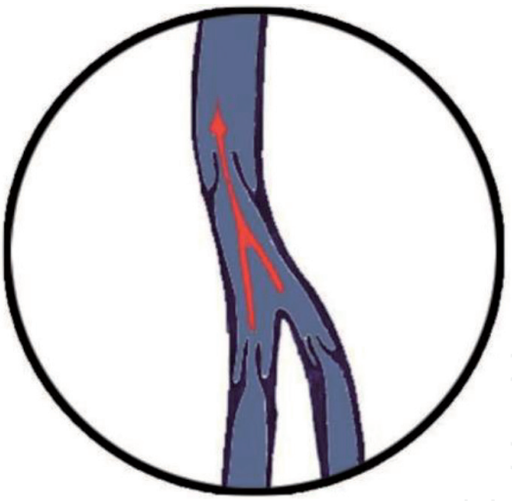

Figure 2.
Normal vein valve.

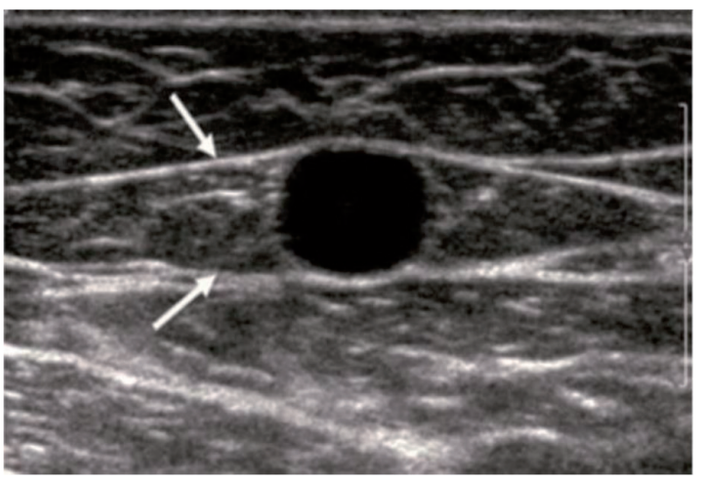

Figure 3.
Ultrasound image of the saphenous compartment.

The perforator veins have normal unidirectional flow from the superficial to deep system, and there are more than 150 perforators in the lower extremities, but most of them are inactive in the normal state. Perforator veins on the medial aspect of the leg represent the most clinically important perforators in chronic vein insufficiency [11].

Valves of lower extremity veins are anatomical features that have clinical importance in cases of incompetence of these valves, transmission of venous pressure to skin venules, and development of skin changes [12].

3. Physiology of lower limb venous system

The venous system functions to support circulation by the venous return mechanism, as 60–80% of blood volume rests in the venous system (25% in the splanchnic network and other residual volumes in postcapillary venules). Therefore, venous return must be equal to cardiac output to maintain homeostasis of tissue perfusion [13]. Many factors have a role in venous return mechanisms, such as central pumps, pressure gradients, venous valves, and muscle pumps (peripheral pumps) [7].

Venous valves are distributed mainly in the distal vein circulation of the lower limb to overcome the effect of gravity and break down the hydrostatic pressure of

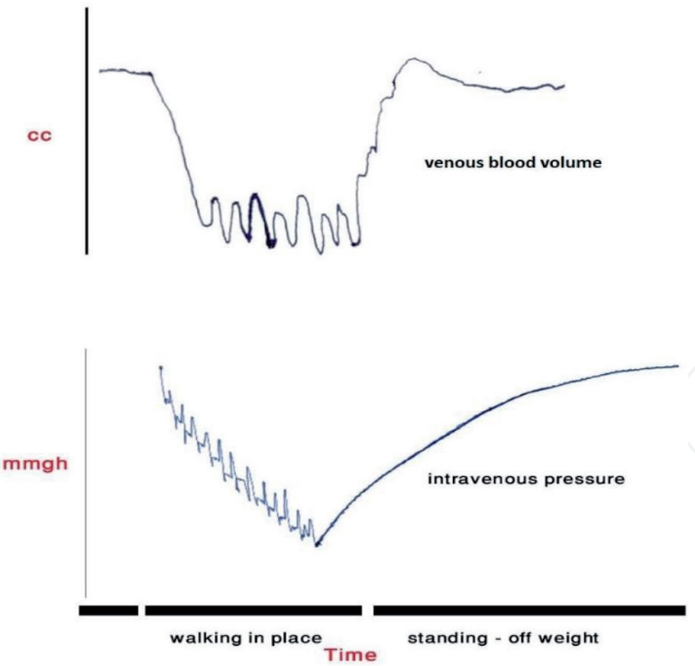

Figure 4.
Schematic summarization of the relationship between pressure and volume in the lower extremities while walking and standing. Note the efficacy of the calf muscle pumping mechanism that leads to a decrease in venous volume and pressure with walking and a slight delay in increasing venous pressure opposite to venous blood volume in the standing position. Alternation in this relationship results in high ambulatory venous pressure.

the blood column into segments. Valve closure is a passive mechanism involving a gradient pressure difference between the supra- and infravalvular segments and normal retrograde flow that lasts for less than 0.5 seconds, which is enough time to close cusps completely [12].

Calf muscle contraction (gastrocnemius and soleus) is an essential part of the mechanism of venous return, and it has been estimated that approximately 60% of venous return from the lower limb depends on the ejection force of the calf muscle. The net result of serial contraction of the calf muscle during exercise produces a streamline and unidirectional blood in the deep venous system toward the heart and improves cardiac output [12].

The efficacy of calf muscle pumps is dependent on the strength of the muscle, range of movement of the ankle joint, and competence of vein valves. We hypothesize that atrophy of the calf muscle decreases the strength of contraction, resulting in a reduction in venous return and chronic vein insufficiency that underlie the pathogenesis of venous ulcers [14].

Accumulation of blood in peripheral venous circulation during rest leads to elevation of venous pressure, especially with the standing position, while contraction of the calf muscle will decrease the venous pressure to a suitable baseline. The measurement of the drop in superficial venous system pressure after exercise is called *ambulatory venous pressure* (AVP), which is an indicator of calf muscle pump function, and an elevation above 30 mm Hg has a linear relationship with leg ulcers (**Figure 4**) [15].

4. Pathophysiology of venous ulcer

The pathophysiology behind chronic leg venous ulcers is still unclear.

Ambulatory venous hypertension (AVH) is the essential pathological factor behind venous ulcers. Venous incompetence can result from immobility, ineffective pumping

mechanisms of the calf muscles, and venous valve dysfunction. In addition, venous valve dysfunction that results from venous thrombosis, phlebitis, or trauma leads to alterations in venous hemodynamics and precipitates venous hypertension [16].

Subsequently, chronic blood stasis of the lower limb venous system causes further capillary damage with inflammatory process activation. Leukocyte activation, endothelial damage, platelet aggregation, and intracellular edema are highly related to venous ulcer development and impaired wound healing [17].

4.1 Ambulatory venous hypertension

The calf muscle pump consists of the calf muscle, a superficial venous system, a deep venous system, and perforators that connect both systems. The out-flow vein of this pump is the popliteal vein. Failure of the calf muscle pump to decrease AVP leads to persistent elevation of postexercise pressure or AVH [15].

Therefore, one or more of the following pathological situations can lead to calf muscle pump dysfunction and AVH.

4.1.1 Reflux in superficial veins system

The cause behind the reflux or incompetent valve in superficial veins is still ambiguous. Currently, there is a discussion on congenital and acquired factors that may be behind the structural changes in valve cusps.

The reflux in superficial veins can be compensated with calf muscle contraction if perforator valves are competent. Secondary incompetent valves of deep and perforator veins are likely to occur with large-volume reflux post sapheno-femoral or sapheno-popliteal incompetence [12].

4.1.2 Reflux/obstruction in deep veins system

Post thrombotic damage to deep veins will result in obstruction, reflux, or both and can even lead to reflux in superficial and perforator veins later (*post thrombotic syndrome*) [12].

4.1.3 Incompetent medial calf perforator

An outward flow of incompetent perforators more than 500 milliseconds and equal to or more than 3.5 millimeters in size will have a significant hemodynamic effect with high AVH and skin changes [12].

Muscular dysfunction of the calf muscle, fixed ankle joint, and prolonged immobilization will lead to blood stasis and venous hypertension as a result of pump mechanism failure [18]. In clinical practice, these pathologies present in combination with multilevel involvement in a large group of patients.

4.2 Chronic venous disorder and chronic venous insufficiency

According to updated terminology of chronic venous disorders in the VEIN-TERM transatlantic interdisciplinary consensus document, chronic venous disorder (CVD) is defined as a wide spectrum of functional and morphological abnormalities that involve the vein system from telangiectasia to venous ulcers (C1–C6 clinical classes). The term chronic venous insufficiency (CVI) is reserved for advanced CVD (C3–C6 clinical classes) and includes moderate to severe edema, skin changes, or venous ulcers [19].

CVI is classified into two types. Primary chronic venous insufficiency occurs due to weakness or degenerative changes in wall or venous valves that started as reflux

in superficial veins and proceed to perforators and deep veins later due to overload that led to dilatation in the venous wall [20].

Secondary chronic venous insufficiency, known as *post-thrombotic syndrome*, is secondary to acute DVT and later sequelae that can lead to reflux, obstruction, or both in deep veins. Additionally, it could be secondary to superficial thrombophlebitis or arteriovenous fistula [19].

4.3 Revised CEAP classification of chronic venous disorders (CVDs)

The need for clinical assessment, evaluation, and stage identification methods of CVD supported the presentation of the CEAP classification at the American Venous Forum annual meeting in 1994, which was revised in 2004 [21].

CEAP classification is a method for categorizing CVD based on:

Clinical manifestations

Ethological factors

Anatomical distribution of disease

Pathophysiological process behind this disorder (**Table 1**)

Clinical class	
C0	No venous disease
C1	Spider angioma
C2	Varicose veins
C3	Edema of venous etiology
C4	Hyperpigmentation, dermatitis, lipodermatosclerosis
C5	Healed ulceration
C6	Active ulceration
Etiology	
Ec	Congenital
Ep	Primary
Es	Secondary
En	No venous etiology identified
Anatomy	
As	Superficial veins
Ap	Perforating veins
Ad	Deep veins
An	No venous location identified
Pathology	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathology identified

[*] Each clinical class is further subclassed as "S" if symptomatic and "A" if asymptomatic.

[*] The symptoms include aching, pain, tightness, skin irritation, heaviness, muscle cramps, and other symptoms relating to venous disorders.

Table 1.
Revised CEAP classification.

5. Epidemiology of venous ulcer

According to the Edinburgh study, a cross-sectional study of a random sample, VLUs represent approximately 70% of all leg ulcers and affect 1% of the population; prevalence increases with age [22].

Development in the diagnosis and early management of varicose veins, especially with significant reflux, can decrease the prevalence of venous ulcers by 50%, as superficial vein insufficiency represents 50% of the causes of leg ulcers. The management of risk factors such as obesity has a strong relationship with venous ulcers [23].

Based on estimates of the San Diego epidemiologic study, more than 11 million men and 22 million women between the ages of 40 and 80 years in the United States have varicose veins, and more than two million adults have advanced CVD with skin changes or ulcers [24]. The incidence of postthrombotic venous ulcers has not changed in the past two decades for women and has recently increased in men [25].

6. Clinical presentation and diagnosis of CVI and venous ulcer

There is a wide spectrum of differential diagnoses for ulcers in the lower limbs. Therefore, proper management depends on determining the etiology of ulcers and managing them. Venous ulcers are the most common cause of lower limb ulcers, followed by arterial and diabetic ulcers. There are distinctive clinical presentation and physical examination findings that can help to differentiate venous ulcers from other lower extremity disorders [26].

The diagnosis of venous ulcers is generally clinical; this step in the diagnosis of venous ulcers is often neglected by physicians. Diagnosis is based on radiology reports such as color duplex ultrasonography and venography, which may be helpful in doubtful cases [27].

Inspection and palpation are essential parts of the examination and should be used to search for signs of venous disorder. Auscultation for bruit is particularly helpful in those with vascular malformation and arteriovenous fistula [27]. Examination is always performed with patients in a standing position and should focus on the size and distribution of varicose veins.

Eklof et al. defined signs present in the clinical part of CEAP classification that suggested CVI (**Figures 5**–7) [21]:

Lower limb edema: Venous hypertension edema unilaterally starts at the ankle and pitting pattern and worsens in the evening.

Eczema: Erythematous dermatitis, which is usually distributed on varicose veins because of uncontrolled CVD but can be seen anywhere in response to local management.

Skin pigmentation: Extravasated blood due to venous hypertension in the small vein leads to intradermal accumulation of hemosiderin, which causes brownish darkening of the skin around the ankle region and sometimes the leg.

Lipodermatosclerosis (LDS): This is defined by Eklof et al. as localized chronic inflammation with fibrosis in skin and subcutaneous tissue and may progress to scarring and contracture in the Achilles tendon [21]. Most authors agree that LDS is highly suggestive of severe CVI and provides clues about the poor prognosis of wound healing. LDS frequently leads to the development of venous ulcers in many cases [18].

Atrophic blanche (white atrophy): This is smooth, white atrophic plaque surrounded by dilated capillary and sometimes hyperpigmentation. It is also a sign of severe CVI and should be distinguished from healed ulcers by history, as it develops

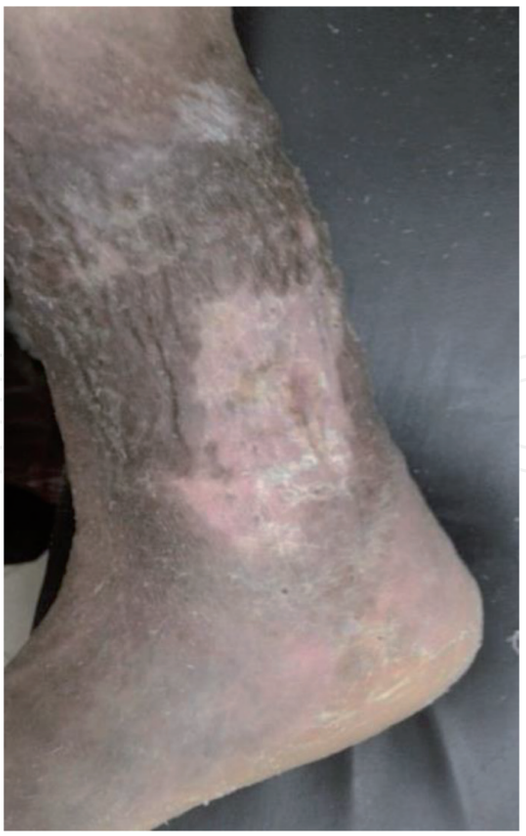

Figure 5.
Atrophie blanche.

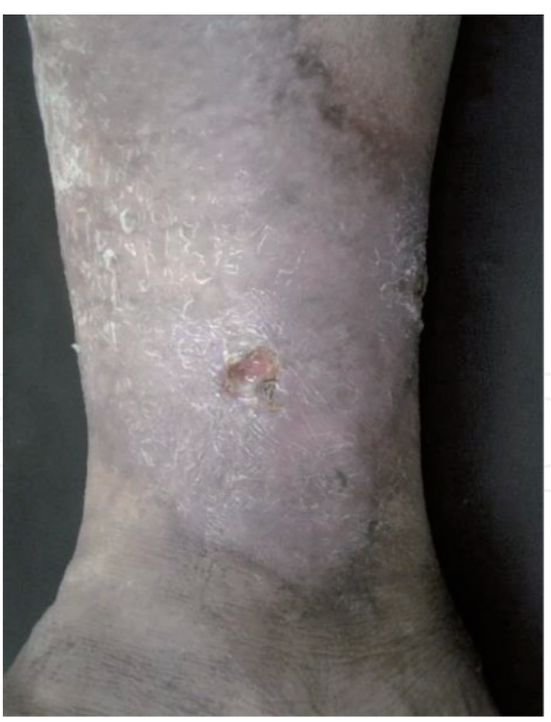

Figure 6.
Lipodermatosclerosis.

independently. Ulcerated atrophie blanche can be extremely painful and has a low tendency for healing [18].

Venous ulcer: Gillespie mentioned the most current updated definition for venous ulcer as *"a full thickness defect of the skin, located in the lower leg, typically with pigmentation and/or skin changes and presence or history of venous disease (documented*

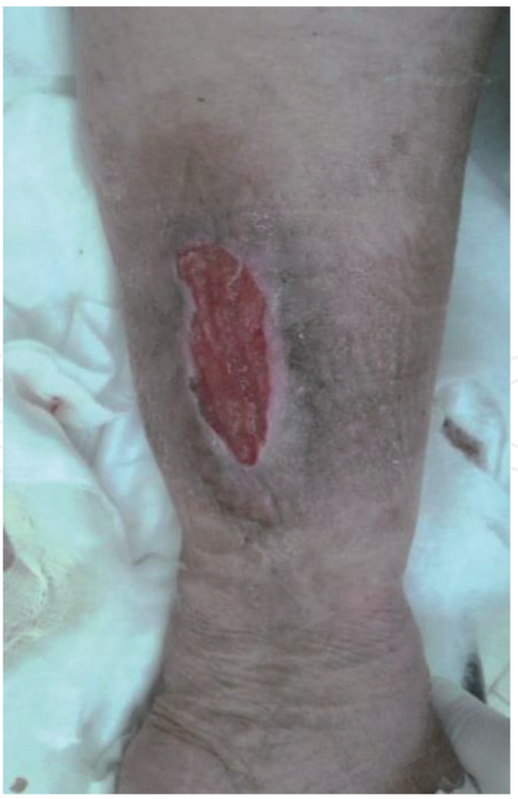

Figure 7.
Eczema.

history of DVT, documented axial venous reflux or deep vein obstruction) in the absence of another condition that could be the essential cause of the ulcer" [28].

A positive history of previous DVT events, family history of varicose veins, or previous intervention to the venous system in line with good clinical examination help to clarify the diagnosis in up to 76% of cases of venous ulcers [18]. The choice of investigation should be based on the severity of the problem and management plan. The noninvasive method is usually used to evaluate patients for venous ablation or preoperative surgery for perforators; invasive diagnostic methods should be used for patients who need complex operations, such as valve reconstruction or venous bypass [12].

The palpable pedal pulse or measurement of ankle-to-brachial blood pressure ratio (ankle/brachial index [ABI]) is one of the critical points in diagnosis of venous ulcer, as it differentiates venous ulcer from arterial ulcer and determines if there is any association of ischemic degree that contraindicated to compression therapy, which is the traditional management approach for venous ulcers. Culture swabs and investigations for vasculitis and connective tissue diseases such as rheumatoid arthritis are helpful in the diagnosis of difficult cases and resistant ulcers [18].

The atypical appearance of ulcers, such as nodular growth, everted edges, deterioration, or delayed healing with appropriate treatment, are indications for biopsy to exclude malignant transformation [29].

Duplex scanning is currently the gold standard for the evaluation of patients with CVIs. It has high sensitivity and specificity in the diagnosis of superficial and deep venous system disorders, and it provides information about the patency of the deep venous system, diameter of the vein, and flow rate. The real-time color duplex scan makes the orientation of venous flow much easier and provides information about reflux in the superficial, deep, or perforator veins. Through interpretation of all previous dates, the differentiation between primary and secondary CVIs is easy. In addition, duplex scans today have an important role in endovenous procedures [23].

Phlebography, such as ascending or descending phlebography, is not a first-line diagnostic tool in cases of venous ulcers and is preserved for evaluation of the venous system before complex procedures such as valve reconstruction or bypass, as it can provide information about the level of obstruction in the deep venous system and the state of valves [23]. CT angiogram is a useful tool for the assessment of the pelvic vein and inferior vena cava (IVC), especially before venous stenting, and MR venogram is preferred for vein malformation cases.

7. Management of venous ulcer

The management of CVUs is a major challenge in terms of healing, preventing recurrence and minimizing social and economic effects. In the Western world, approximately 1% of the annual healthcare balance is expended on venous ulcer care [22]. The future world vision directed more towards the prevention rather than the management of venous ulcers becomes more expensive over time, thus standing in the way of the 2009 Pacific Vascular Symposium's goal to decrease incidence of venous ulcer by 50% in the next 10 years [30].

The key for the management of venous ulcers is reduced AVH, which leads to a decrease in edema and inflammatory reactions in the leg, resulting in stimulated healing of ulcers and preventing recurrence if optimum venous pressure is maintained. The correction of vein disorders that lead to venous hypertension is an important step in addition to ulcer care [31]. The management of venous ulcers includes conservative (lifestyle modification, compression therapy, and ulcer care) and surgical (surgical cover of ulcer and surgical elimination of venous hypertension) procedures.

7.1 Conservative management

7.1.1 Modification of lifestyle

Theoretically, moderate exercise concentrated on mobility of the ankle joint and contraction of the calf muscle (peripheral heart) are beneficial in decreasing venous congestion of the lower limbs and hemodynamics. Although there is not a lot of evidence confirming the effect of exercise on healing venous ulcers, supervised moderate exercise should be considered as adjuvant to main treatment for CVI and venous ulcer.

Another important procedure that is not practical for patients is leg elevation at or above the level of the heart, which can decrease venous pressure around the ankle nearly to zero, resulting in an improvement in lower limb swelling and an increased ulcer healing rate. Leg elevation, if associated with compression therapy, can decrease ulcer recurrence [31].

7.1.2 Compression therapy

Compression therapy is still the cornerstone of CVI and venous ulcer care. It is defined as an applied external pressure on a specific lower limb area to overcome gravity and hydrostatic pressure in veins. The mechanism of action has not been fully understood until now. It depends on preserving interfacing pressure and stiffness (increase of interface pressure with activity as increased limb circumference by muscle contraction).

In applying compression to a patient in a normal standing position, an external pressure of 35–40 mmHg will narrow the vein; however, if pressure exceeds

60 mmHg, it will lead to occluding of the vein. As such, optimum external graduated pressure between 35 and 40 mmHg will improve venous pumping function and microcirculation. In addition, it lowers the level of inflammatory mediators, such as alpha tumor necrosis factor, which causes tissue damage. Therefore, compression promotes ulcer healing [31].

The Unna boot developed in 1885 is the oldest modality of compression therapy. Other more familiar modalities include compressive bandages, compression stockings, and intermittent pneumatic devices. LaPlace's law states that the pressure in the cylinder is inversely related to the radius with uniform tension on the wall, so this modality of compression will provide graduated pressure that is the highest at the ankle, resulting in the cephalic direction of venous flow [32].

A recent Cochrane review found that venous ulcers heal more rapidly with the application of compression therapy than without compression therapy and that high-grade compression with a three- or four-layer bandage or short stretch bandage is better than other systems that deliver low pressure [33].

A meta-analysis out of the United Kingdom found that high-grade compression (sub-bandage pressure 35–40 mmHg at ankle) by standardized four-layer bandage technique shows shorter healing time than short stretch bandages [34]. The average healing rate is approximately 60–70% at 12–24 weeks in various types of compression models [35].

Brien et al. stated that four-layer bandaging is the most effective method for the management of venous ulcers, with a healing rate of 54% at 3 months in a randomized control trial conducted on 200 patients. In addition, they recommend using it routinely in the management of patients with uncomplicated venous ulcers. Additionally, it can decrease the rate of recurrence if maintained lifelong [36].

The following sections discuss the technique and components of these systems, also known as the *Charing Cross Hospital Bandage*, according to recommendations from the Scottish Intercollegiate Guidelines Network (SIGN) guidelines [37] and the International Leg Ulcer Advisory Board (**Figure 8**) [38].

First layer: The padding layer involves application of orthopedic cotton in a spiral fashion with minimal overlap from the base of toes to just under the knee to protect the bony prominence and absorb exudate. In patients with ankle circumference less than 18 cm, an additional layer is needed as an artificial increase in circumference.

Second layer: This is a layer of cotton crepe bandage that oversmooths the first layer and has the last effect in compression. It is applied in a spiral fashion with 50% overlap.

Figure 8.
Component of four-layer bandaging. (1) Orthopedic cotton; (2) cotton crepe bandage; (3) elastic extensible bandage; and (4) elastic cohesive bandage.

Third layer: This is an elastic extensible bandage applied by figure eight winding with 50% extension from base of toes to just under the knee (it provides sub-bandage pressure = 17 mmHg). The ankle joint is kept in dorsiflexion or at a 90-degree angle.

Fourth layer: This layer is an elastic cohesive bandage applied in a spiral fashion with 50% overlap and 50% extension (adds remaining 23 mmHg sub-bandage pressure) (**Figure 9**).

The disadvantage of the four-layer compression bandage is that it needs trained physicians to apply the optimum pressure, whereas compression stockings can be used by the patient and removed at night [39].

Intermittent pneumatic compression is expensive and requires immobilization of the patient. Therefore, it is reserved for bedridden patients who cannot tolerate continuous compression therapy [40].

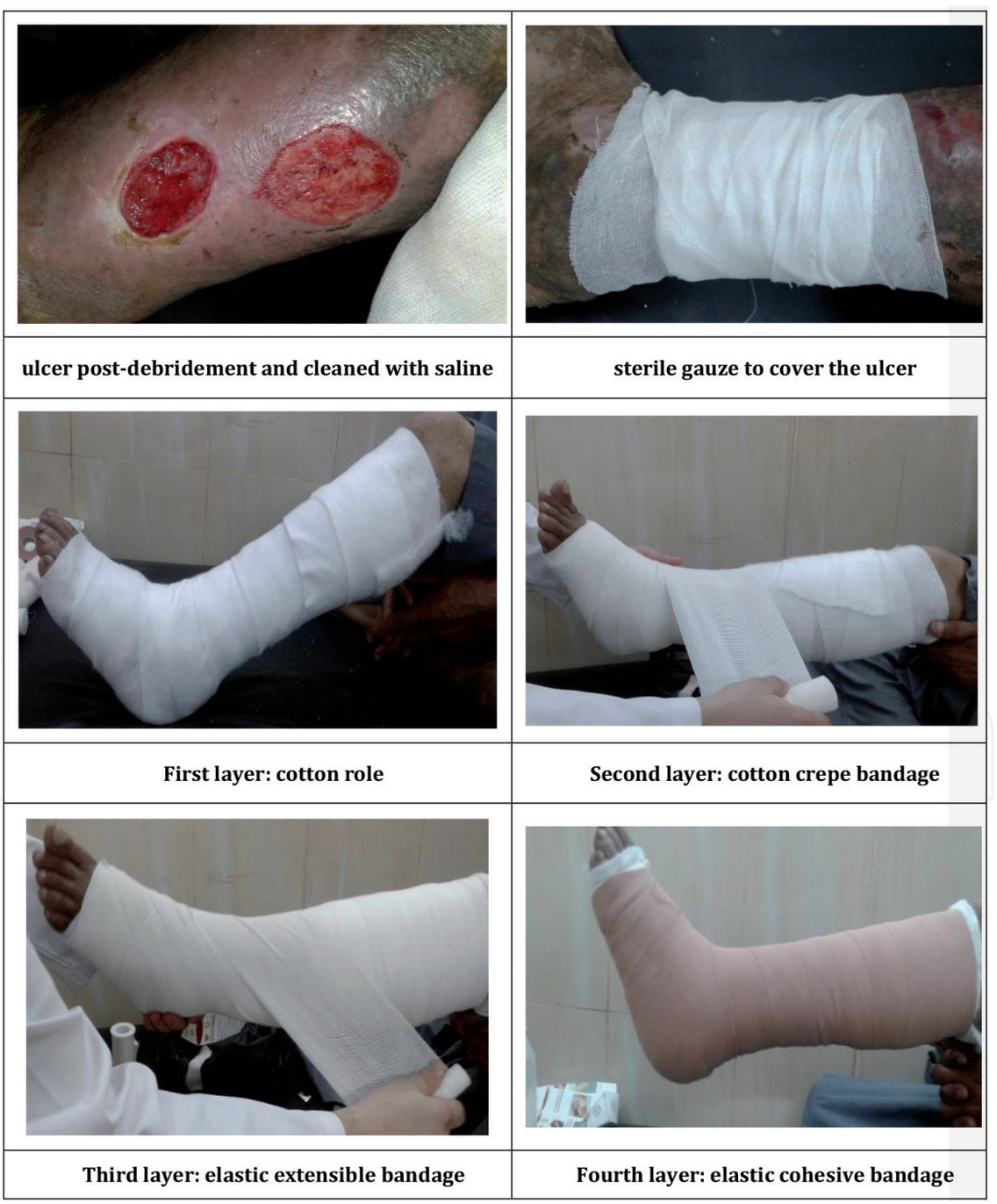

Figure 9.
Four-layer compression bandaging steps.

7.1.3 Ulcer care

Tap water can be used to clean venous ulcers. There is no advantage observed with the use of physiological saline and recommended deep debridement for recalcitrant chronic venous leg ulcers to remove fibrosis that arrests the healing process, but the use of chemical or enzymatic debridement has no special advantage [23].

A meta-analysis of 42 randomized controlled trials showed no major difference between dressing types and expensive hydrocolloid dressings. Medical evidence does not support increased healing with hydrocolloid dressings compared to lower-cost, simple nonadherent dressings. Without clear evidence that supports the use of certain dressings over others, the choice of dressings for venous ulcers can be directed by cost, ease of application, and patient and physician preference [41].

There is no evidence to support that the use of topical antibiotics has a positive effect on the management of infected venous ulcers or promotes healing. A Cochrane review on the use of silver-containing topical material concluded that there is insufficient evidence to support its use in infected venous ulcers. Other articles support avoiding topical application because it sensitizes the skin and recommend managing clinically infected venous ulcers with systemic antibiotics [29].

7.2 Surgical management

7.2.1 Surgical cover of ulcer (skin graft)

Skin grafting may be used for patients with large or refractory venous ulcers that do not show signs of healing within 4–6 weeks with standard care [29]. However, skin grafting is not effective if there is persistent edema, which is common with venous insufficiency, and the underlying venous disease is not addressed. A Cochrane review found few high-quality studies to support the use of skin grafting for the treatment of venous ulcers [42].

7.2.2 Surgery for venous insufficiency

The role of surgery is to reduce venous hypertension, promote healing, and prevent ulcer recurrence. Surgical options for the treatment of venous insufficiency include ablation of the saphenous vein, interruption of the perforating veins with subfascial endoscopic surgery, stenting of iliac vein obstruction, and removal of incompetent superficial veins with phlebectomy, stripping, sclerotherapy, or laser therapy [43].

Scottish guidelines state that there is no evidence to support surgical intervention for venous insufficiency prior to standard management (compression) for healing venous ulcers. One study showed a significant difference in recurrence in favor of surgery [23].

7.3 Platelet concentrates

Platelet concentrates are autologous material prepared from venous blood after various processing of blood samples. Generally, it depends on the centrifugation principle to separate the whole blood sample into red blood cells that heavily precipitate down and concentrate other elements that can be used topically or via infiltration for therapeutic purposes [44].

Platelet concentrates were first presented 20 years ago and were developed with the aim of using blood protein elements as a biological source of growth factors to promote the angiogenesis process and stimulate cells involved in the healing process, such as fibroblasts, neutrophils, and mesenchymal stem cells [45].

Platelet-rich fibrin (PRF) is a natural fibrin matrix developed by Choukroun et al. in France through new technology that is characterized by a simple and open access technique without anticoagulant or bovine thrombin. Just immediate centrifugation of patients' blood samples leads to conversion of fibrinogen to fibrin by physiological thrombin; this slow polymerization of fibrin charges it by platelets, leucocytes, and cytokines to give us autologous biomaterials from platelets and immune cells to support healing [46].

The protocol for preparing PRF is very simple. Blood is extracted from the patient and placed in a glass-coated tube without anticoagulant and immediately centrifuged. Time is an important factor, as the coagulation cascade starts within minutes via activation of platelets through contact with the glass tube in absence of an anticoagulant. Then, physiological thrombin transforms the fibrinogen to a fibrin network charged with active platelets and cytokines that will take the middle portion of the tube between the precipitated red blood cells layer at the bottom and acellular plasma at the top [47].

Any delay in blood handling will lead to the start of coagulation without separation of the blood component, and fibrin will be formed in a diffuse way in all tubes, resulting in a blood clot and not a PRF clot (**Figures 10–12**) [48].

From clinical data, note the ability of PRF to induce healing without any inflammatory excess. Dohan et al. stated that the PRF process not only activates platelets but also activates leucocytes to release important cytokines in response to artificial inflammation induced by these techniques. An initial investigation revealed that PRF also functions as an immune node to increase defense mechanisms and control inflammatory responses, which explains the decrease in surgical site infection treated by PRF because of trapped cytokines in fibrine networks [49].

PRF contains three main components that are important to tissue healing.

The first of these components is the host cells, which constitute the main difference between PRF and previous-generation PRP, as PRF incorporates not only platelets but also incorporates active leucocytes that have a role in anti-infection and regulation of immunity. The natural three-dimensional fibrin network is a

Figure 10.
Centrifuge device used for PRF.

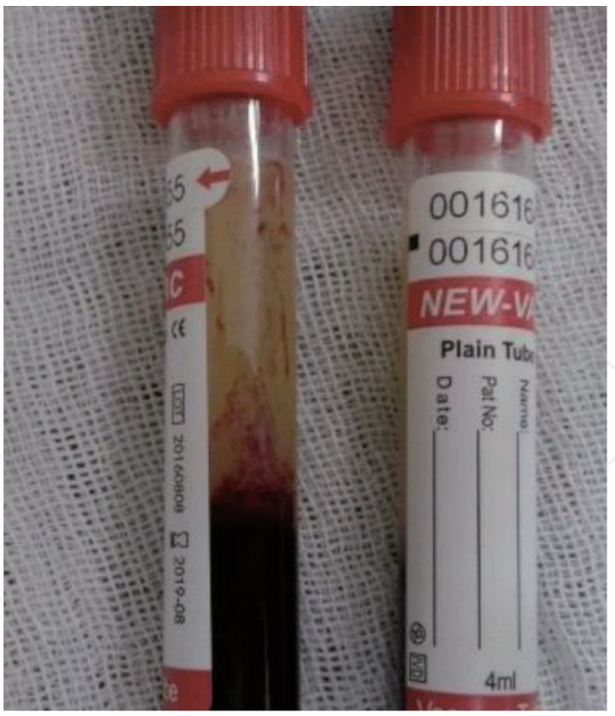

Figure 11.
PRF clot at middle of tube.

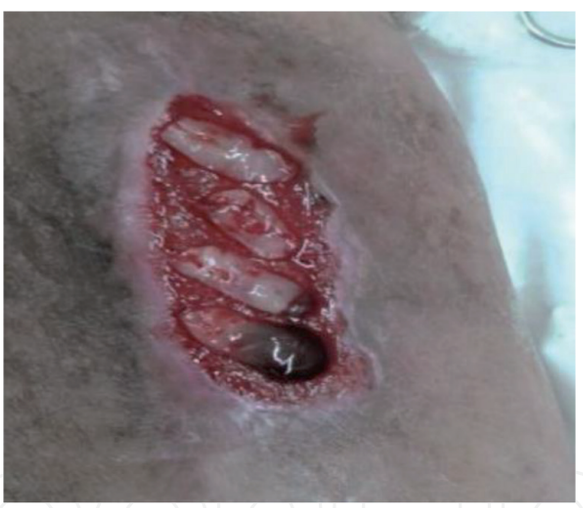

Figure 12.
PRF membranes on the surface of the ulcer.

second component that does not work as a server for host cells only but can also promote cell invasion and help in tissue regeneration. The last items in these structures are the natural growth factors that have an important biological role in the healing process, as platelet-derived growth factor (PDGF) is an essential growth factor for cell migration, differentiation, and proliferation. Vascular endothelial growth factor (VEGF) is also important for the angiogenesis process in granulation tissue, and other growth factors, such as TGF-beta, epidermal growth factor, and insulin-like growth factor, are important for wound healing (**Figures 13** and **14**) [45, 50].

Yazawa et al. stated that the concentration of growth factors in PRF was three times greater than that in PRP due to the use of fibrine as a drug delivery system for growth factors, which helped in the slow release of natural factors over a period of approximately 1 week [51].

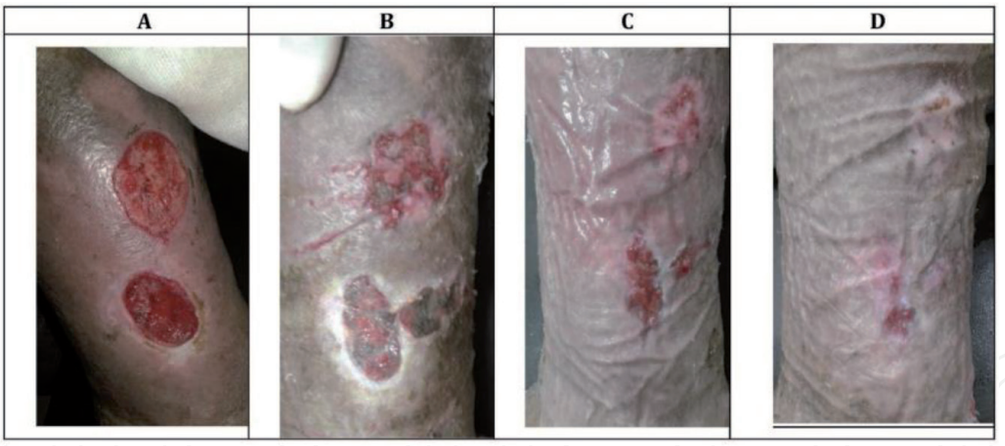

Figure 13.
A male patient, 45 years old, with secondary CVI of the left leg with two ulcers treated with four-layer compression bandages and PRF membrane applied on the proximal ulcer only.

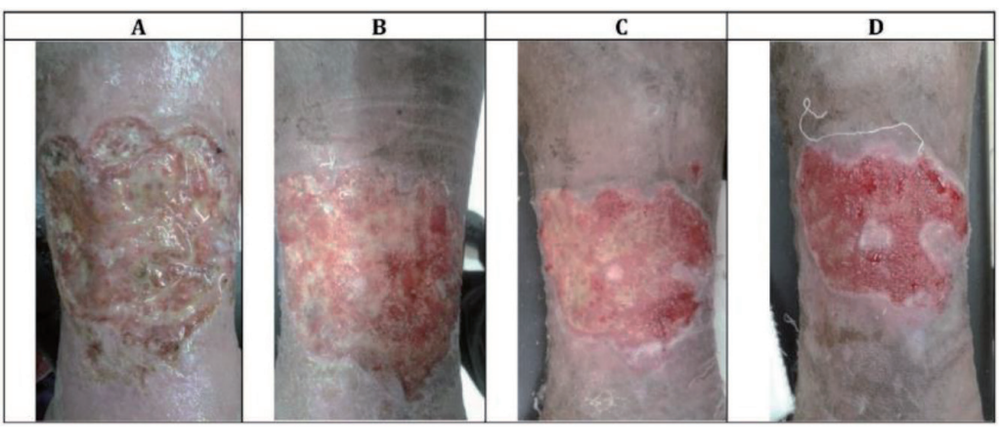

Figure 14.
A 55-year-old female patient with primary CVI of the left leg with ulcers treated with four-layer compression bandages and PRF.

8. Conclusion

- Venous ulcers are the most common cause of CLUs and have a great impact on patient QoL and productive work time.
- Management depends on reversing ambulatory venous hypertension, which is the essential pathological factor behind VLUs, by using compression therapy as the cornerstone of management along with new adjuvant therapies that can provide necessary growth factors to promote the healing process.
- PRF is a promising material for wound healing, as platelets and leukocytes release many growth factors and cytokines that are important for wound healing.

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Conflict of interest

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Author details

Walid A.M. Ganod
Vascular Surgery Unit, Zliten Medical Center, Zliten Medical College, Asmarya Islamic University, Zliten, Libya

*Address all correspondence to: walid.ganod@gmail.com

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