Chapter

Chronic Venous Ulcer

Walid A.M. Ganod

Abstract

This research review is endeavoring to shed the light on the cause and effect of Chronic Venous Ulcer (CVU) in line with its therapeutic procedures. In the last two decades, a lot of the changes occurred in strategy of wound management through developing adjunctive therapy that supported wound healing. Eventually, the latest development was in platelet concentration technology produced the platelet-rich fibrin (PRF). It was categorized as the 2nd generation of platelet concentration family after Platelet Rich Plasma (PRP). Considering that Venous Leg Ulcers (VLUs) accounted for 70% of all leg ulcers and estimated one percent of the population where age as an essential factor has increased its prevalence. The chronicity and refractory nature of venous ulcer had a great effect on the quality of life and work productivity of patients apart from, the expenditure of significant amount of medical resources and efforts. Therefore, the ultimate goal of (VLU) management was to induce a rapid healing without recurrence which mainly helped to improve the quality of life (QoL). The first therapeutic procedure used in treatment of VLU was compression therapy where the application of effective graduated compression decreased the overload in venous system and venous reflux. Furthermore, it accelerated the capillary of blood flow and decreased the capillary of fluid leakage which in return alleviated the limb edema.

Keywords: Venous ulcer, Ambulatory venous hypertension, Chronic venous insufficiency, Compression therapy, Platelet rich fibrin

1. Introduction

Chronic leg ulcers (CLUs) defined as a chronic wound that does not show tendency of healing within reasonable period, this period can determine the state of being chronic wound or not as if there is no tendency of healing after 3 months or not fully healed after 12 months, it will be named as chronic ulcer [1]. The aforementioned period is not a fixed number it is governed by other factors such as ulcer ethology, size and other factors [2].

In general ulcer can be described in many different ways for instance, it has a full thickness wound, it lacks a source of re epithelization in the center, and it shows a low tendency of healing.

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

The Wound Healing Society described the chronic wound as “a silent epidemic disorder” correlated to percentage of public had this condition. In the US, as an approximate number of 6.5 million patients suffered from chronic non healed wounds. Therefore, two million of working days lost annually. In addition, in the UK it has estimated an annual incidence of leg ulcer by 3.5 per one thousand individuals [4].
Venous insufficiency considered as the most common cause of the leg ulcers with a percentage of 70%. Inline arterial diseases, mixed venous & arterial disorders represent 10% and 15% respectively. There is a big challenge in assessment and diagnosis for CLU where it comes to having miscellaneous disorders such as vasculitis, hematological diseases. This kind of disorders represents the last 5% of the causes of CLUs [5].

Scottish Guidelines defined the chronic venous leg ulcer as “an open lesion between the knee and the ankle joint that remains unhealed for at least four weeks and occurs in the presence of venous disease” [6].

2. Anatomy of venous system in lower limb

The anatomical variation and nonuniform nomenclature of lower limb veins system especial in literatures were supported the constitution of International Interdisciplinary Committee at 2001 to did adjustment and uniform the anatomical terminology of lower limb veins (Figure 1) [7].

The veins of lower limb can be classified into three systems, superficial, deep and perforators veins. These veins are arranged into two main compartments; superficial and deep compartments. Superficial compartment is presented between the skin and muscular fascia which contain the superficial veins, On the other hand, deep compartment that contain the deep veins is presented under the deep fascia. The perforator veins are connected the superficial and deep system [9]. Ultrasound image shows there is other compartment within the superficial compartment enclosing the saphenous vein named a saphenous compartment (Figures 2 and 3).

The principle way for venous return from lower limb is through the deep vein system which paired below the knee and accompany to arteries then joined to form popliteal vein that complete ascending as femoral vein. The main veins in superficial system that target for a lot of venous therapy are the great saphenous vein

![Diagram superficial venous system of lower limb](image-url)
and small saphenous vein, these veins are connected together with communicator veins difference to perforator veins that connect the superficial and deep system by perforating the muscular fascia [10].

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

Valve of lower extremity veins is one of anatomical feature that has clinical important in case 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

Venous system offers the most important function to support circulation by venous return mechanism as 60–80% of blood volume resting in venous system
(25% in splanchnic network & other residual volume in post capillary venules). Therefore, the venous return must be equals to cardiac output to keep homeostasis of tissue perfusion [13]. There are many factors had a role in venous return mechanism such as: central pump, pressure gradient, venous valves and muscle pumps (peripheral pump) [8].

Venous valves distributed meanly in distal vein circulation of lower limb to overcome the effect of gravity and breakdown the hydrostatic pressure of blood column into segments, the closure of valve is passive mechanism by gradient pressure difference between supra & infra valvular segment and normal retrograde flow that last for less than 0.5 sec. That enough for closure of cusps completely [12].

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

Efficacy of calf muscle pump is depended on strength of muscle, range of movement of ankle joint and competent of vein valves. Hypothesis the atrophy of calf muscle decreases the strength of contraction result in reduction of venous return and chronic vein insufficiency that standing behind the pathogenesis of venous ulcer [14].

Figure 4.
Schematic summarization of relationship between pressure & volume in lower extremity with walking and standing position. Note the efficacy of calf muscle pumping mechanism that lead to drop of venous volume and pressure with walking and slight delay in raising of venous pressure opposite to venous blood volume at standing position. Alternation in this relationship resulting in high ambulatory venous pressure.
Accumulation of blood in peripheral venous circulation during rest leads to elevation of venous pressure especially with standing position while contraction of the calf muscle will decrease the venous pressure to be suitable base line. The measuring of drop in superficial venous system pressure after exercise called ambulatory venous pressure (AVP) which is indicator for calf muscle pump function and it is elevation above 30 mm Hg has linear relationship with leg ulcer (Figure 4) [15].

### 4. Pathophysiology of venous ulcer

The pathophysiology behind chronic leg venous ulcers is still unclear. Ambulatory venous hypertension (AVH) is considered to be the essential pathological factor behind venous ulcer. Venous incompetence can be resulted from immobility, ineffective pumping mechanism of the calf muscles and venous valves dysfunction. In addition, venous valves dysfunction that is resulted from venous thrombosis, phlebitis or trauma will lead to alternation in venous hemodynamic and precipitate venous hypertension [16]. Subsequently, chronic blood stasis of lower limb venous system causes further capillary damage with inflammatory process activation. Leukocyte activation, endothelial damage, platelet aggregation, and intracellular edema highly related to venous ulcer development and impaired wound healing [17].

#### 4.1 Ambulatory venous hypertension

Calf muscle pump consists of calf muscle, superficial venous system, deep venous system and perforators that connect both systems. The out flow vein of this pump is popliteal vein. Failure of calf muscle pump to decrease AVP leads to persistent elevation of post exercise pressure that referred to as ambulatory venous hypertension (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 structure changes in valve cusp. The reflux in superficial veins can be compensated with calf muscle contraction if perforator valves are competent, Secondary incompetent valve of deep and perforator veins likely to occur with large volume reflux post sapheno-femoral or sapheno-popliteal incompetence [12].

##### 4.1.2 Reflux/obstruction in deep veins system

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

##### 4.1.3 Incompetent medial calf perforator

If out ward flow of incompetent perforators more than 500 milliseconds and equal to or more than 3.5 millimeter in size will have significant hemodynamic effect as high AVH and skin changes [12].
Muscular dysfunction of 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 presented in combination with multilevel involvement in 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) defined as a wide spectrum of functional and morphological abnormality that involves veins system from telangiectasia to venous ulcers (C1- C6 Clinical classes). Chronic venous insufficiency (CVI) term reserved for advanced CVD (C3-C6 clinical classes) that include moderate to severe edema, skin changes or venous ulcer [19].

**CVI classified into two types:**
- **Primary chronic venous insufficiency**: occur due to weakness or degenerative changes in wall or venous valves which started as reflux in superficial veins and

| Clinical class | Description |
|----------------|-------------|
| 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 |

*Each clinical class is further sub classified as “S” if symptomatic & “A” if asymptomatic
* The symptoms include aching, pain, tightness, skin irritation, heaviness, muscle cramps, and other symptoms relating to venous disorders

| Etiology | Description |
|----------|-------------|
| Ec       | Congenital |
| Ep       | Primary |
| Es       | Secondary |
| En       | No venous etiology identified |

| Anatomy | Description |
|---------|-------------|
| As      | Superficial Veins |
| Ap      | Perforating Veins |
| Ad      | Deep Veins |
| An      | No venous location identified |

| Pathology | Description |
|-----------|-------------|
| Pr        | Reflux |
| Po        | Obstruction |
| Pr,o      | Reflux & obstruction |
| Pn        | No venous pathology identified |

**Table 1.**
*Revised CEAP classification.*
proceed to perforators and deep veins later due to overload that lead to dilatation in the venous wall [20].

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

### 4.3 Revised CEAP classification of chronic venous disorders (CVD)

The need for clinical assessment, evaluation and stage identification method of CVD supported to present of CEAP classification on American Venous Forum annual meeting 1994 and revised on 2004 [21].

CEAP classification is a method for classification of CVD based on:
- Clinical manifestations.
- Ethological factors.
- Anatomical distribution of disease.
- Pathophysiological process behind this disorder (*Table 1*).

### 5. Epidemiology of venous ulcer

According to Edinburgh study which was a cross-sectional study of a random sample, the venous leg ulcers represents an approximate 70% of all leg ulcers and estimates 1% of the population with a prevalence that increases with age [22].

Development in diagnosis and early management of varicose vein especially with significant reflux can decrease prevalence of venous ulcer by 50% as superficial vein insufficiency represent 50% of causes of leg ulcers. The management of risk factors as obesity had great relationship with venous ulcers [23].

On the basis of estimates of the San Diego epidemiologic study, more than 11 million of men and 22 million of women between the ages of 40 and 80 years in the United States have varicose veins, as well as more than two millions of adults have advanced CVD with skin changes or ulcers [24]. The incidence of post-thrombotic venous ulcers has not changed in the past two decades for women and it recently increases in men [25].

### 6. Clinical presentation and diagnosis of CVI and venous ulcer

There is a wide spectrum of differential diagnosis for ulcer in lower limb. Therefore, the proper management depends on determine the etiology of ulcer and manage it. Venous ulcer constitutes the most common cause of lower limb ulcers followed by arterial & diabetic ulcer. There are distinctive clinical presentation and physical examination findings which can help to differentiate venous ulcers from other lower extremity disorder [26].

The diagnosis of venous ulcers is generally clinical; this step in diagnosis of venous ulcer is neglected by physicians and they are based on radiology report only as color duplex ultrasonography and venography that may be helpful in doubtful cases [27].

Inspection and palpation are essential parts of the examination and should be searched on signs of venous disorder, auscultation for bruit is particularly helpful in those with vascular malformation and arteriovenous fistula [27]. Examination always done with patient in a standing position and should focus on size and distribution of varicose veins.
Specific signs for CVI:

*Eklof* and his team have defined signs present in the clinical part of CEAP classification that suggested CVI *(Figures 5–7)* [21]:

**Lower limb edema:** the edema of venous hypertension unilateral, start at ankle, pitting pattern and becomes more worse at evening.

**Eczema:** Erythematous dermatitis, that is usually distribute on varicose vein a result of uncontrolled CVD, but can be seen anywhere in response to local management.

**Skin pigmentation:** extravasated blood due to venous hypertension in small vein leads to accumulation of hemosiderin intradermal that the causes behind Brownish darkening of skin around ankle region and sometime leg.

**Lipodermatosclerosis (LDS):** defined by *Eklof* as a localized chronic inflammation with fibrosis in skin and subcutaneous tissue and may progress to scarring & contracture in tendo Achilles [21]. Most of author agree that LDS is highly suggestive of sever CVI and gives clue about bad prognosis of wound healing. LDS frequently proceed the development of venous ulcer in a lot of cases [18].

**Atrophie blanche (white atrophy):** smooth white atrophic plaque surrounded by dilated capillary and hyperpigmentation some times. It is also sign of sever CVI and should be distinguished from healed ulcers by history as develop independently. Ulcerated atrophie blanche can be extremely painful and have 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 5. Atrophie blanche.](image)
Figure 6.
Lipodermatosclerosis.

Figure 7.
Eczema.
Recent Advances in Wound Healing

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

Positive history of previous DVT event, family history of varicose vein or previous intervention to venous system in line with good clinical examination help to clarify the diagnosis in up to 76% of cases of venous ulcer [18]. the choice of investigation should be based on severity of problem and management plan, It is usually use the non-invasive method to evaluate patient for venous ablation or pre-operative surgery to perforator and keep invasive diagnostic method to patient need complex operation 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 differentiate it from arterial ulcer and determine if there is any association of ischemic degree that contraindicated to compression therapy, the traditional management to venous ulcer. The culture swab and investigations for vasculitis and connective tissue diseases such as rheumatoid arthritis helpful in diagnosis of despiteful cases and resistant ulcer [18].

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

Duplex scan is currently the golden standard for evaluation of patient with CVI, with high sensitivity & specificity in diagnosis of superficial and deep venous system disorders, it gives information about patency of deep venous system, diameter of vein and flow rate. The real time color duplex scan makes orientation of venous flow much easier and provides information about reflux in superficial, deep or perforator vein, through interpretation all previous dates the differentiation between primary and secondary CVI be easy. In addition, duplex scan today had an important role in endovenous procedure [23].

Phlebography such as ascending or descending phlebography are not diagnostic tools of first choice in case of venous ulcer and preserved for evaluation of venous system before complex procedure as valve reconstruction or bypass as it can provide information about level of obstruction in deep venous system and state of valves [23].

CT Angiogram useful tool for assessment of pelvic vein and inferior vena cava (IVC) especially before venous stenting, MR Venogram preferred to vein malformation cases.

7. **Management of venous ulcer**

The management of chronic venous ulcer constitutes one of the most major health challenge on side of healing, prevent recurrence and minimize social and economic effect. In western world, approximately 1% of annual health care balance expended on venous ulcer care [22]. The future world vision directed toward the prevention of incidence of venous ulcer more than their management that becomes more expensive through time, that is standing on goal of Pacific Vascular Symposium 2009 that talked on globally decrease incidence of venous ulcer by 50% in next 10 years [30].

The key for management of venous ulcer is reduced ambulatory venous hypertension (AVH) that leads to decrease of edema and inflammatory reaction in leg result in stimulate healing of ulcer and prevents recurrence if maintained optimum venous pressure. The correction of vein disorder that leads to venous hypertension is an important step beside ulcer care [31]. The management of venous ulcer includes: **conservative part** (life style modification, compression therapy and ulcer...
care) and surgical part (surgical cover of ulcer and surgical elimination of venous hypertension).

7.1 Conservative management

7.1.1 Modification of life style

Theoretically moderate exercise concentrated on mobility of ankle joint and contraction of calf muscle (peripheral heart) thought to be benefit in decrease venous congestion of lower limb and hemodynamics, despite there is no enough study about the effect of exercise on healing of venous ulcer but supervised moderate exercise should be considered as adjuvant to main treatment for CVI and venous ulcer.

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

7.1.2 Compression therapy

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

In normal standing patient application an external pressure of 35–40 mmHg will narrow the vein but if pressure excessed 60 mmHg it will lead to occluding of vein, so optimum external graduated pressure between 35 and 40 mmHg will improve venous pumping function and microcirculation. In addition, it is lowering the level of inflammatory mediator as alpha tumor necrosis factor which cause tissue damage. Therefore promotes ulcer healing [31].

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

The recent Cochrane review found that the venous ulcer heals rapidly with application of compression therapy than without and high graded compression by 3 or 4 layer bandage or short stretch bandage better than other system that deliver low pressure [33].

High graded compression (sub bandage pressure 35–40 mmHg at ankle) by standardized four layer bandage technique that used in UK show shorter time needed for healing than short stretch bandage in meta-analysis of randomized trial [34]. With average healing rate approximate 60–70% at 12 to 24 weeks by various type of compression model [35].

The Brien et al. stated that the four layer bandaging is the most effective method for management of venous ulcer with healing rate 54% at three months in randomized control trial that conducted on 200 patients. In addition, he recommend to use it routinely in management of patient with uncomplicated venous ulcer. Also it can be decrease rate of recurrence if maintained lifelong [36].
According to recommendation of SIGN guidelines (Scottish Intercollegiate Guidelines Network) [37] & International Leg Ulcer Advisory Board the technique and component of these system that also known as Charing Cross Hospital Bandage include (Figure 8) [38].

**First layer:** (padding layer) orthopedic cotton role applied in spiral fashion with minimal overlap from base of toes to just under the knee to protect the bony prominence and absorb exudate, in patient with ankle circumference less than 18 cm additional layer needed as artificial increase of circumference.

**Second layer:** (cotton crepe bandage) that over smooths the first layer and has the last effect in compression, applied in spiral fashion with 50% overlap.

**Third layer:** elastic extensible bandage applied by figure of eight winding with 50% extension from base of toes to just under the knee (It provide sub bandage pressure = 17 mmHg). The ankle joint kept in dorsiflexion or at 90° angle.

**Fourth layer:** elastic cohesive bandage, it’s 2nd layer of compression, applied in spiral fashion with 50% overlap & 50% extension (adds remaining =23 mmHg sub bandage pressure) (Figure 9).

The disadvantages of the four -layers compression bandage is that they need trained physician to apply the optimum pressure in against to compression stockings that self-used and can be removed at night [39].

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

**7.1.3 Ulcer care**

We can use the tap water for cleaning venous ulcer. There is no advantage observed by use of physiological saline and recommended to deep debridement for recalcitrant chronic venous leg ulcers to remove fibrosis that arrest healing process, but use of chemical or enzymatic debridement have no special advantage [23].

A meta-analysis of 42 randomized controlled trials have showed no major difference between dressing types and the expensive hydrocolloid dressings. it is not getting high medical evidence support use it as a healing benefit over the lower-cost simple nonadherent dressings. Without clear evidence that support the use of dressing type over another, the choice of dressings for venous ulcers can be directed by cost, ease of application, patient and physician preference [41].
There is no evidence support that the use of topical antibiotic has positive effect on management of infected venous ulcers or promote healing. A Cochrane review on use of silver containing topical material concluded that there is no insufficient evidence to support use it in infected venous ulcers. Other articles support to avoid topical application as it sensitize the skin, as well as a recommendation to manage clinical infected venous ulcer by the use of 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 does not show sign of healing within 4–6 weeks with stander 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 recent
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 treatment of venous insufficiency include ablation of the saphenous vein; interruption of the perforating veins with sub-fascial endoscopic surgery; stenting of iliac vein obstruction and removal of incompetent superficial veins with phlebectomy, stripping, sclerotherapy or laser therapy [43].

Scottish guidelines stated that there is no evidence to support the surgical intervention for venous insufficiency should be prior to standard management (compression) for healing of venous ulcer and the available study showed significant difference in recurrence in favor for surgery [23].

7.3 Platelet concentrates

Platelet concentrates are autologous material prepared from venous blood after various processing of blood samples. Generally, it depend on centrifugation principle to separate the whole blood sample into red blood cells that heavy so precipitated down and concentrate other element that can be used by topical or infiltration for therapeutic purposes [44].

Platelet concentrates that first has presented since 20 years ago and it was developed on aim of using blood protein elements as a biological source of growth factors that able to promote the angiogenesis process and stimulation of cells involved in healing process as fibroblast, neutrophils and mesenchymal stem cells [45].

Platelet Rich Fibrin: This is a natural fibrin matrix that developed by Choukroun’s et al. In France, through new technology that characterized by simple and open access technique without anticoagulant or bovine thrombin. Just immediate centrifugation of patients’ blood sample that lead to conversion of fibrinogen to fibrin by physiological thrombin, this slow polymerization of fibrin charged it by platelets, leucocytes and cytokines to give us autologous biomaterial from platelets and immune cells support healing of process [46].

The protocol for prepare of PRF is very simple: blood extracted from patient in glass coated tube without anticoagulant and immediate centrifuged and here time factor is so important as coagulation cascade started within minutes by activation of platelets through contact with glass tube in absent of anticoagulant then physiological thrombin transform the fibrinogen to fibrin net-work charged with active platelets and cytokines that will take the middle portion of tube between the precipitated red blood cells layer in bottom by effect of centrifuge device and acellular plasma in top [47]. Any delay in blood handling will lead to start coagulation without separation of blood component and fibrin will be formed in diffuse way in all of tube result in blood clot not PRF clot (Figures 10–12) [48].

From clinical date note the ability of PRF to induce healing without any inflammatory excess. Dohan et al. stated the PRF process not only activate the platelet but also leucocytes to release important cytokines in response to artificial inflammation induced by these technique. Initial investigation revealed the PRF working also as immune node for increase defense mechanism and control inflammatory response that explain the decrease of surgical site infection which treated by PRF due to effect of trapped cytokines in fibrine net-work [49].

The PRF contains three main components that are important to tissue healing. The first of these components is the host cells which constitute main difference...
between PRF and previous generation PRP as PRF is not only platelets, but it’s also incorporate active leucocytes that had a role in anti-infection and regulation of immunity, natural three dimension fibrin net-work is second component which
Figure 12.
PRF membranes on the surface of ulcer.

| A | B | C | D |
|---|---|---|---|
| ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |

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

| A | B | C | D |
|---|---|---|---|
| ![Image](image5.png) | ![Image](image6.png) | ![Image](image7.png) | ![Image](image8.png) |

Figure 14.
a female patient, 55 years old, with primary CVI at left leg with ulcer that treated by four layer compression bandages and PRF.

| A | B | C | D |
|---|---|---|---|
| ![Image](image9.png) | ![Image](image10.png) | ![Image](image11.png) | ![Image](image12.png) |
not work as server for host cells only but had the ability to promote cell invasion and helped in tissue regeneration. The last item in these structure is the natural growth factors that had an important biological role in healing process as PDGF is an essential growth factor for cell migration, differentiation and proliferation, also VEGF which is important for angiogenesis process in granulation tissue, other growth factors as TGF-beta, epidermal growth factor and insulin-like growth factor that are important to wound healing (Figures 13 and 14) [45, 50].

Yazawa et al. stated that the concentration of growth factors in PRF three times more than in platelet-rich plasma (PRP) due to use of fibrine as drug delivery system for growth factors, more over it help in slow release of that natural factors over a period of one week approximately [51].

8. Conclusion

- Venous ulcers are the most common cause of chronic leg ulcers with high impact on patients’ quality of life and productive work time.

- The management depends on reversing the ambulatory venous hypertension which is the essential pathological factor behind the VLUs by using the compression therapy the corner stone of management along with new adjuvant therapies that able to provide necessary growth factors to promote healing process.

- Platelet-rich fibrin (PRF) is promising material for wound healing as the platelets and leukocytes release many growth factors and cytokines that important for wound healing.

Acknowledgements

Staff of Scientific board of Vascular Surgery Department, Faculty of Medicine-Zagazig University-Egypt.
Rwida Nori Alati – Zliten medical college – Asmarya Islamic University.

Conflict of interest

No conflict of interest.
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

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Kahle B, Hermanns H-J, Gallenkeren G. Evidence-Based Treatment of Chronic Leg Ulcers. Dtsch Arztebl Int 2011; 108: 231-237.

[2] Mostow EN. Diagnosis and classification of chronic wounds. Clin Dermatol 1994; 12: 3-9.

[3] Mekkes JR, Loots MAM, Van Der Wal AC, et al. Causes, investigation and treatment of leg ulceration. Br J Dermatol 2003; 148: 388-401.

[4] Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: A major and snowballing threat to public health and the economy: PERSPECTIVE ARTICLE. Wound Repair Regen 2009; 17: 763-771.

[5] Sarkar PK, Ballantyne S. Management of leg ulcers. Postgrad Med J 2000; 76: 674 LP – 682.

[6] O’Donnell TF, Passman MA, Marston WA, et al. Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. J Vasc Surg 2014; 60: 3S–59S.

[7] Caggiati A, Bergan JJ, Gloviczki P, et al. Nomenclature of the veins of the lower limb: Extensions, refinements, and clinical application. 2005; 719-724.

[8] Bergan JJ, Bunke N. The vein book. Oxford University Press, 2014.

[9] Radiology I. Ultrasonographic anatomy of the lower extremity superficial veins. 2012; 423-430.

[10] Bergan J, Pascarella L. Venous Anatomy, Physiology, and Pathophysiology. 2006; 39-45.

[11] May R, Partsch H SJ. Perforating veins. Mu `nchen: Urban and Schwarzenberg; 1st ed. 1980.

[12] Vaidyanathan S, Menon RR, Jacob P, et al. Chronic Venous Disorders of the Lower Limbs: A Surgical Approach. Springer, 2014.

[13] Gloviczki P. Handbook of venous disorders: Guidelines of the American venous forum third edition. CRC Press, 2008.

[14] Jane B, Helen E, Kathleen F, et al. Understanding the relationships between the calf muscle pump, ankle range of motion and healing for adults with venous leg ulcers: a review of the literature. 20.

[15] Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg 2007; 46:S: 4-24.

[16] Araujo T, Valencia I, Federman DG, et al. Managing the patient with venous ulcers. Ann Intern Med 2003; 138: 326-334.

[17] Etufugh CN, Phillips TJ. Venous ulcers. Clin Dermatol 2007; 121-130.

[18] Valencia IC, Falabella A, Kirsner RS, et al. Chronic venous insufficiency and venous leg ulceration. J Am Acad Dermatol 2001; 44: 401-424.

[19] Eklof B, Perrin M, Delis KT, et al. From the American Venous Forum Updated terminology of chronic venous disorders: The VEIN-TERM transatlantic interdisciplinary consensus document. YMVA 2009; 49: 498-501.

[20] Labropoulos N, Tassiopoulos AK. Vascular diagnosis of venous thrombosis. In: Vascular diagnosis. Elsevier, 2005, pp. 429-438.

[21] Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004; 40: 1248-1252.
[22] Lal BK. Venous ulcers of the lower extremity: Definition, epidemiology, and economic and social burdens. 2015; 35-37.

[23] Charit C, Schulze B. S3-Guideline on Venous Leg Ulcer Developed by the Guideline Subcommittee ‘Diagnositics and Treatment of Venous Leg Ulcers’ of the European Dermatology Forum Evidence-based. 2016; 1843-1875.

[24] Kaplan RM, Criqui MH, Denenberg JO, et al. Quality of life in patients with chronic venous disease: San Diego population study. J Vasc Surg 2003; 37: 1047-1053.

[25] Smith JJ, Garratt AM, Guest M, et al. Evaluating and improving health-related quality of life in patients with varicose veins. J Vasc Surg 1999; 30: 710-719.

[26] McGee S, Boyko E. Physical examination and chronic lower-extremity ischemia: A critical review. Arch Intern Med 1998; 158: 1357-1364.

[27] BRADBURY A, RUCKLEY CV. Clinical presentation and assessment of patients. In: Handbook of Venous Disorders: Guidelines of the American Venous Forum Third Edition. CRC Press, 2008, p. 331.

[28] Gillespie DL. Venous ulcer diagnosis, treatment, and prevention of recurrences. J Vasc Surg 2010; 52: 8S–14S.

[29] Thomas F, Jr OD, Passman MA, et al. Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery Ô and the American Venous Forum. 2014; 3-59.

[30] Henke P. The pacific vascular symposium 6: the venous ulcer summit in perspective. J Vasc Surg 2010; 52: 1S–2S.

[31] Pascarella L, Shortell CK. Medical management of venous ulcers. Semin Vasc Surg 2015; 28: 21-28.

[32] Rudolph D. Standards of care for venous leg ulcers: Compression therapy and moist wound healing. 2001; 20-27.

[33] Cullum N, Nelson E, Fletcher A, et al. Compression for venous leg ulcers (Review). 2008.

[34] O’Meara S, Tierney J, Cullum N, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients. The BMJ; 338. Epub ahead of print 2009. DOI: 10.1136/bmj.b1344.

[35] Raffetto JD, Marston WA. Venous ulcer: what is new? Plast Reconstr Surg 2011; 127 Suppl: 279S–288S.

[36] Brien JFO, Grace PA, Perry IJ, et al. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. 2003; 794-798.

[37] Guidelines SI. Management of chronic venous leg ulcers A national clinical guideline. Epub ahead of print 2010. DOI: 10.1136/thx.2008.097741.

[38] Moffatt C, Rabe E. POSITION Understanding compression. EWMA, and MEP 2003; 19.

[39] Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Arch Dermatol 1998; 134: 293-300.

[40] Nelson E, Mani R, Thomas K, et al. Intermittent pneumatic compression for treating venous leg ulcers (Review).

[41] Palfreyman S, Nelson EA, Michaels JA. Dressings for venous leg ulcers: systematic review and meta-analysis. Bmj 2007; 335: 244.
[42] Jones JE, Nelson EA. Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev*; 2.

[43] Robson MC, Cooper DM, Aslam R, et al. Guidelines for the treatment of venous ulcers. *Wound Repair Regen* 2006; 14: 649-662.

[44] David M, Ehrenfest D, Andia I, et al. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. *Muscle, Ligaments Tendons J* 2014; 4: 3-9.

[45] Miron RJ, Choukroun J. *Platelet Rich Fibrin in Regenerative Dentistry: Biological Background and Clinical Indications*. John Wiley & Sons, 2017.

[46] Saluja H, Dehane V, Mahindra U. Platelet-Rich fibrin: A second generation platelet concentrate and a new friend of oral and maxillofacial surgeons. *Ann Maxillofac Surg* 2011; 1: 53.

[47] Toffler M, Toscano N, Holtzclaw D, et al. Introducing Choukroun’s platelet rich fibrin (PRF) to the reconstructive surgery milieu. *J Implant Adv Clin Dent* 2009; 1: 21-30.

[48] Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I: Technological concepts and evolution. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology* 2006; 101: 39-44.

[49] Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part III: Leucocyte activation: A new feature for platelet concentrates? *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology* 2006; 101: 51-55.

[50] Ehrenfest DMD, Corso M Del, Diss A, et al. Three-Dimensional Architecture. 81. Epub ahead of print 2009. DOI: 10.1902/jop.2009.090531.

[51] Yazawa M, Ogata H, Nakajima T, et al. Basic studies on the clinical applications of platelet-rich plasma. *Cell Transplant* 2003; 12: 509-518.