Chronic Venous Insufficiency and Venous Ulcers: Pathophysiology

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Contents

Introduction

Progression of a clinical Class 2 venous disease to higher classes is an unpredictable but unfortunate event in the natural history of chronic venous disorders (CVD). It is not an essential event in all patients with CVD. Only a subset of patients go through this process. The triggering factors responsible for this transformation are not well understood. It is a slow degenerative process taking months and years. But when it does happen, the venous reflux which initially commenced in the superficial system extends to involve the deep veins and the perforators. Other symptoms such as edema (C3), venous eczema/lipodermatosclerosis (C4), and ulcers (C5–6) also become prominent. The term, primary chronic venous insufficiency (CVI) or simply CVI, is used to denote this condition. It includes the clinical classes from C3 to C6. Venous hypertension with microcirculatory impairment is the root cause for the clinical manifestations. The intensity of the morbidity associated with CVI was comparable with those seen in congestive cardiac failure and chronic lung disease [1].

There is another category of patients with almost identical clinical manifestations, secondary chronic venous insufficiency, resulting from post-thrombotic damage to deep veins. This is a late sequel of acute deep vein thrombosis (DVT). It is an acquired inflammatory pathology resulting in reflux, obstruction, or a combination of both in the deep veins. Involvement of the superficial

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veins is a late event [2, 3]. It is commonly known as the *post-thrombotic syndrome* and is discussed in detail in Chap. 14. This chapter would focus on the pathophysiology of CVI. The following aspects would be reviewed:

- *Risk factors for ulceration in CVI*
- *The stages and location of the lesions*
- *Structural changes in the veins and other tissues*
- *Molecular events*

Risk Factors for Ulceration in CVI

Venous ulcer is the end stage in the evolution of chronic venous insufficiency. It is reported that venous ulcers affect around 1 % of the population during their lifetime [4]. Considering the prolonged and expensive treatment of venous ulcer, it will be more prudent to prevent the ulcers in the first setting itself. Identification of the risk factors for ulceration in a patient with varicose veins is essential for undertaking any such preventive strategies. Several population-based epidemiological studies focusing on the risk factors for varicose veins are available. Some studies have focused on the risk factors for ulceration in patients with established varicose veins [4, 5]. The etiology of venous ulcer is certainly multifactorial. Some of these may be related to the venous disease per se. A number of disease-unrelated factors are also identified for the causation of ulcers. A brief review of these conditions is presented.

Venous Disease-Related Risk Factors for Ulceration

- *Presence of skin changes* such as lipodermatosclerosis, corona phlebectatica, and dermatitis in a patient with varicose veins aggravate the risk of ulceration [4]. These findings indicate an advanced clinical class of CEAP classification. The extent and severity of the varices were also reported to be significant. Forty-nine percent of patients with ulcer had grade III varicose veins (extensive/severely symptomatic varicose veins – Basle classification), whereas only 33 % of the non-ulcerated limbs had grade III varices [4].
- *Reflux in deep veins* was found to be associated with higher incidence of ulceration. Of special interest is the status of the popliteal valve. Reflux in the popliteal vein is associated with a high incidence of ulceration [4]. In our experience, combined superficial, deep, and perforator incompetence (multisystem disease) is an important factor rather than involvement of an isolated segment. More than 50 % of our patients had reflux involving all the three systems.
- *Failure of the microvenous valves* in the small superficial veins along with degenerative changes in the small vessel network is being identified as a key to the skin changes including ulceration. It has been demonstrated that valvular incompetence can extend even up to the sixth-generation tributaries. Degeneration and valve failure are required at both the larger proximal vessels and the small superficial veins for the development of skin changes including ulceration. This issue is discussed later on in this chapter.
- *DVT in patients with varicose veins* increases the risk for ulceration by 25.7 times [5]. In the study reported by Robertson et al., 28 % of patients with ulceration had a positive history of DVT or pulmonary embolism. The figure for the group without ulceration was 8 % [4]. Varicose veins patients have a slightly increased risk of developing DVT (5.6 %) compared to general population (0.9 %) [6]. Deep vein reflux is a common finding in patients with C3 to C6 classes. Primary valvular incompetence (PVI) is one of the pathologies for such reflux. In this subset of patients, distal DVT are not uncommon below the refluxive valve [7]. Many of these episodes of DVT can be silent and asymptomatic, and these patients can present with late symptom of leg ulceration.

Disease-Unrelated Factors

- *Age and gender*. Generally, venous ulcers are observed at fairly advanced age. The mean

age for ulceration reported in one of the studies was 59 years [5]. For the non-ulcerated group, the mean age was lower by 10 years. In the same study, 60 % of patients with ulcers were men [5]. In contrast, for varicose veins, there is a female dominance. The Edinburgh vein study has also reported a higher incidence of CVI among men [8]. In our series, the mean age of the patients with ulceration was 57.10 years. We have also observed a higher male incidence among our CVI patients; 54.2 % of our patients with CVI were men.

- *Increased BMI*. Obesity (BMI 30 or more) is a significant risk factor for ulceration [4, 5]. But there are conflicting reports on this issue.
- *Cigarette smoking* was associated with a greater risk of ulceration. Those who smoked between 10 and 19 cigarettes per day were 1.8 times more likely to develop an ulcer [4, 5].
- *Prolonged standing* is a significant factor in the pathogenesis of CVD in general. But there is no evidence to show that this increases risk of ulceration [4]. More importantly many patients were found to be sedentary with low levels of physical exercise. Physical activity stimulates the calf muscle pump and reduces the venous hypertension [4].
- *Deficiency of calf muscle pump* function in CVI has been extensively reported. Whether calf muscle pump impairment is the cause or effect of CVI is a debatable issue. This is discussed in detail later in this chapter.
- *Restricted mobility of ankle joint* can contribute to and aggravate calf muscle pump dysfunction. Patients with ulcers demonstrated reduced dorsiflexion of the ankle joint, compared to normal controls [4]. Here again the cause-effect relationship is difficult to establish.
- *Comorbidities*. The incidence of heart diseases, diabetes, and hypertension was higher in the ulcerated group compared to the non-ulcerated group [5]. This could be related to the more advanced age of this group of patients.
- *Associated leg injury*. In one of the published reports, history of major trauma to the leg such as fractures was not uncommon in the group of patients with varicose veins and ulceration [5]. This in turn can be a risk factor for clinical or subclinical DVT. It is pointed out that major trauma to the leg in patients with varicose veins increases the risk of ulceration by 4.7 times compared to those without any major injury [5].
- *Genetic predisposition to venous leg ulcers* is an area of relatively recent interest. In a study conducted in Italian population, Zamboni and group have reported that in patients with CVD, the presence of hemochromatosis C282Y gene mutation consistently increases the risk of developing venous leg ulceration. In post-thrombotic disease, this association was not observed. The authors have recommended testing this mutation to screen high-risk patients of CVD and select them for early interventions to prevent ulceration [9]. Yet another mutation studied extensively was the coagulation factor XIII. But no correlation was observed between mutations of coagulation factor XIII and leg ulceration. In fact, the presence of factor XIII Leu 34 and Leu 564 was associated with smaller ulcer surface area and may indicate a favorable prognosis [10].

Stages and Location of Lesions in CVI

The structural and functional changes in the lower limb venous system alter the normal venous hemodynamics and result in venous hypertension. This is the root cause of CVI [11, 12]. Traditionally, the term venous stasis syndrome was used to describe the changes in the skin and soft tissues of lower leg. This was under the mistaken belief that venous stasis is the primary pathology in these patients. But now, it is well-recognized that venous hypertension is the key factor; CVI is the preferred term rather than venous stasis syndrome. Several stages are identified in the evolution of skin lesions in CVI: [2, 12].

- Corona phlebectatica. This is also known as ankle flare or malleolar flare and is considered to be an early sign of advanced venous disease. It presents as a fan-shaped pattern of numerous intradermal veins on the medial or lateral aspect of ankle and extends toward the

foot. This results from dilatation of the intradermal venules due to the increased venous pressure. The apex of the flare is in relation to an incompetent perforator. The venous hypertension is transmitted through this vessel. It fans out toward the sole of the foot.

- Eczema and pigmentation present as an erythematous dermatitis progressing to blistering, weeping, or scaling eruption of the skin of the leg. This can be associated with brownish dark pigmentation of the skin. The venules are thin walled and cannot withstand the high pressure. They rupture and the blood extravasates into the tissues. The resultant hemosiderin pigments are responsible for the itching and discoloration.
- Venous lipodermatosclerosis (LDS). This is a sign of severe disease and is characterized by localized chronic inflammation and fibrosis of skin and subcutaneous tissue of the lower leg. It can produce fibrosis and contracture of the tendoachilles. The lesion can present as an acute or chronic form; the latter is more common. Pathologically it is a form of sclerosing panniculitis. This lesion is also in relation to an incompetent perforator, and through that it is connected to the main venous systems of the lower limbs. LDS is located over the site of maximum venous hypertension.
- Stage of ulceration. This is a full-thickness defect of the skin commonly located around the ankle region. The ulcer fails to heal spontaneously and is sustained by the CVD. The ulcer is also in relation to the medial calf perforating veins (Fig. 11.1).

These lesions of CVI are typically located in the skin and subcutaneous tissue around the ankle joint, an area known as ulcer-bearing area or gaiter area [12]. This area extends from the lower border of the soleus muscle to the ankle. The impact of the ambulatory venous hypertension is experienced maximally at this site. Several anatomical features make this area vulnerable [12].

- This region is located farthest from the heart and has therefore a high venous pressure even in normal persons. In subjects with CVD, the pressure is further elevated due to the venous pathology.

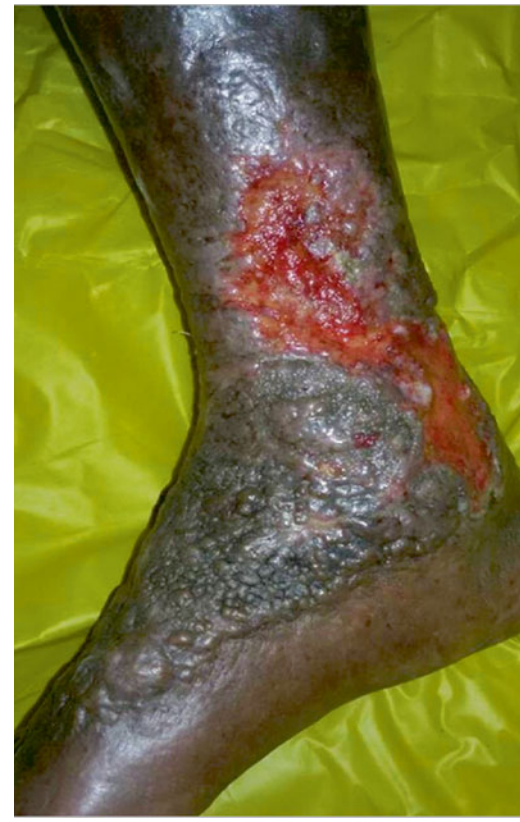

Fig. 11.1 Venous ulcer with lipodermatosclerosis. Fixed ankle joint

- The area has a relatively poor arterial supply.
- The action of the foot muscle pump can produce an extra load in this area. The venous flow in the foot is from deep to superficial veins when the foot muscle pump acts [13–15]. In a patient with defective calf muscle pump, this extra load around the ankle may create a strain.

Structural and Functional Changes in CVI

Failure of the calf muscle pump and impaired venous return from lower extremity generate venous hypertension. It is now accepted that venous ulcer cannot exist in the presence of a normally functioning calf muscle pump. Calf muscle pump function can be adversely affected

in the presence of structural or functional changes in several systems and locations. These locations are enumerated below:

- Reflux in the venous systems
- Nonthrombotic iliac vein lesion
- Changes in the calf muscles
- Changes in the deep fascia
- Ankle joint dysfunctions
- Changes in the lymphatic system

Reflux in the Venous System

Venous reflux is the most consistent structural change observed in patients with CVI. Reflux commences in the superficial veins, and as the clinical class progresses, it extends to the perforator and the deep systems.

Reflux in the superficial venous system is the initial event in primary CVI. Venous ulcers are considered to be rare in patients with isolated superficial vein reflux, but 15.2–20 % of patients had isolated superficial vein incompetence only [16, 17]. Ulceration is commonly observed when reflux exists in both superficial and deep systems. Robertson et al. reported that in 43 % of patients with ulceration, there was combined superficial and deep vein reflux [4]. As already mentioned, CVI primarily and predominantly affects the superficial system [3].

Incompetent medial calf perforators are considered to be an important factor in the genesis of venous ulcer. They can produce a high pressure leak of blood from the deep to superficial vein during the contraction of the calf muscles producing ambulatory venous hypertension [18–20]. An incompetent calf perforator is considered significant, only when the calf muscle pump is defective or when there is pathology in the deep veins [21]. Objective findings of such pathological perforators include outward flow duration more than 500 ms and size equal to or more than 3.5 mm [22]. Incompetent perforators in a C2 class of patient revert to normal when the superficial reflux is eliminated.

Reflux in the deep veins, along with superficial and communicating vein incompetence, is a common finding in patients with venous ulcers (C6 class) [23–25]. Deep vein reflux is seen in less than 10 % in C2 class in comparison to 70 % in C6 class [3]. Two causes are suggested for reflux in the deep veins, the valve theory and the wall theory [26].

The valve theory suggests that reflux results from a thrombotic or nonthrombotic pathology. The most widely identified etiology for the damage and destruction of valves in the deep veins is post-thrombotic pathology. The nonthrombotic cause for deep vein valve failure was first identified and described by Robert Kistner. He coined the term primary vein valve incompetence (PVI) for this condition. In this condition, the valve cusps are stretched and elongated, floating freely in the vein lumen. The two cusps fail to meet and close in the midline, thus permitting reflux [23]. These changes are predominantly located in the proximal segments. Many etiological factors are suggested for this: wear and tear, phlebitis, connective tissue defects, etc. [26]. PVI can develop in the deep veins in discontinuous segments. The failure of deep vein valves may not happen in a sequential ascending or descending fashion [26].

The wall theory: The basic problem here is circumferential dilatation of the vein wall at the level of valve apparatus. The valve cusps are normally formed, but because of the increase in luminal circumference, they fail to meet across and close the vein lumen. Several factors are suggested for this defect. They include phlebitis and defect in the connective tissue framework [26].

Irrespective of the cause, reflux in deep veins impairs the lower limb venous return. In normal individuals, the calf muscle pump along with the competent valves ensures a streamlined, unidirectional cephalad flow in the deep veins. When there is reflux in the deep veins, this is converted into a bidirectional, turbulent, up and down movement – the "yo-yo" effect (Fig. 3.5). The net effect is volume overload leading on to hypertension in the deep venous system. The perforator and superficial systems become incompetent secondary to this overload – the safety valve effect. The crucial factor in genesis of leg ulcer is the status of the popliteal vein valve. When this is competent, ulceration is rare even with extensive disease. On the other hand, incompetence of this valve results

in ulceration. Hence, the popliteal valve is referred to as the gatekeeper [4]. Lim and colleagues have tried to define the precise clinical and hemodynamic significance of deep vein reflux (DVR) while controlling reflux in the superficial system. The study included 3,222 limbs in 2,349 patients using duplex ultrasound, CEAP classification, and venous filling index (VFI). According to them, DVR to the level of the knee and calf is associated with more severe disease irrespective of reflux in superficial veins [25].

Isolated involvement of a single system is extremely rare in clinical practice. According to Raju, multisystem multilevel reflux is more pathological than a single-system single-level reflux [24]. Our experience has been the same; 58 % of our patients had combined reflux in the superficial, perforator, and deep systems.

Reflux in the microvenous valves is now in the center stage. Till recently, it was believed that valves do not exist in veins <2 mm in diameter. This is now disproved. Reflux in the smaller venous tributaries is now recognized as an important factor in the pathogenesis of skin lesions in CVI. Microvenous valves can exist up to the sixth-generation tributaries with the third generation forming the boundary in pathological states. Failure of microvalves is shown to be a key factor for skin changes. Such changes can be present even in the absence of reflux within the GSV or its branches. Macro- and microvessel involvement when combined aggravates the severity of the lesions [27]. Sometimes even with extensive varices, some patients do not develop skin problems. This could be explained by the presence of competent microvalves especially in the third-generation boundary venules. These vessels are inaccessible for surgical intervention. There is robust evidence to show that foam sclerotherapy can obliterate them.

Nonthrombotic Iliac Vein Lesion

Nonthrombotic iliac vein lesion (NIVL) results from extraluminal compression of the left common iliac vein. The vein is compressed at its commencement by the right common iliac artery. This is a permissive lesion which requires another pathology such as trauma, cellulitis, edema, etc., to become clinically manifested. This condition is also known as May-Thurner syndrome and is being increasingly identified in a large number of CVD patients. The pathology can be totally corrected by endovenous stenting [28]. This is the only condition of primary CVI where obstruction of the deep vein is identifiable.

Calf Muscle Changes in CVI

Structural changes in the calf muscles are identified in a number of patients with CVI. The clinical relevance of such findings is not properly understood. Significant functional impairment of the calf muscles was reported by Yang and his colleagues in 1999 [29]. Diminished calf muscle pump function is reported as a risk factor for ulceration in patients with varicose veins [4]. Biopsy and electron microscopic study of gastrocnemius muscle in patients with CVI has demonstrated several structural changes [30]. The changes correlated with ambulatory venous pressure (AVP) findings [30]. A recent study has reported increased calf muscle deoxygenation in patients with CVI [31]. It has been proposed that, rather than the calf muscle impairment resulting from CVI, the poor calf muscle itself may be responsible for pump failure in some patients with leg ulceration [4]. It has been reported that calf muscle pump function and dynamic calf muscle strength improved in a group of CVI patients after 6 months of structured exercise [32]. Such structured exercise program has been suggested as an adjuvant to mainstream treatment in patients with CVI [32].

Changes in the Deep Fascia of the Leg

The deep fascia of the leg has a major role in the calf muscle pump mechanism. Patients who have undergone emergency fasciotomy for traumatic conditions are reported to have impaired calf

muscle pump function leading onto CVI [33]. Similar changes have been reported in a group of patients who have undergone elective fasciotomy for chronic exertional compartment syndrome [34].

Ankle Joint Dysfunction

Limitation of ankle joint movement is a risk factor for the development of ulcers in patients with varicose veins [4]. Two findings noted in patients with nonhealing venous ulcers are restricted movements at ankle joint and calf muscle wasting [35]. The relevance of ankle joint mobility on venous ulcer healing and calf muscle pump function has been emphasized by several workers [36–38] (Fig. 11.1).

Changes in the Lymphatic System

Absorption of interstitial fluid and lymph is markedly disrupted adjacent to venous ulcer bed. Lymphatics were found to be absent in the ulcer bed and were present only sporadically in the intermediate zone [39].

The exact significance of these structural and functional alterations in the different locations is not fully understood. Whether they are the cause or the effect of CVI is also a debatable issue. It is well understood that these changes affect the calf muscle pump adversely and aggravate the venous hypertension setting in a vicious cycle. Correcting these changes would break the vicious cycle and improve the calf muscle function.

Molecular Events in Chronic Venous Insufficiency

The external manifestations of CVI are only the proverbial tip of the iceberg. At the cellular and molecular levels, a complex cascade of events is identified. Lim and Davies [26] and Perrin and Ramelet [40] have reviewed these complex changes, and the following is a summary based on their report.

Venous inflammation is a key factor in producing vein wall and valve damage, leading onto venous hypertension. The venous hypertension in turn causes further damage, setting in motion a self-propagating process. The changes involve the wall and the valves of the macro veins (the superficial and to some extent the deep veins). The changes in the macrovessels affect the microcirculation and finally the target tissue of CVI, the skin over the gaiter area. Thus, one can identify the molecular events at three levels: macrovessels, microcirculation, and dermal tissues.

The changes in the macrocirculation affect the vein wall and the valves. They commence from the venous endothelium. Areas of intimal hypertrophy with increased collagen content alternate with hypotrophic segments, with few smooth muscle cells (SMC) [26, 41]. The extracellular matrix (ECM) proteins are broken down, mostly by the action of the enzyme matrix metalloproteinases (MMPs). Venous hypertension is a stimulus for the upregulation of MMPs. The activity of MMPs is inhibited by several tissue inhibitors of MMPs (TIMPs).

MMP-TIMP imbalance is reported in patients with CVD [42]. The smooth muscle cells become dedifferentiated from a contractile to secretory phenotype and lose their ability to contract [43]. Apoptosis becomes dysregulated. These events result in dilatation and relaxation of the veins along with loss of venous tone. Repeated postural stress from prolonged standing leads to pooling of blood and more distortion of valves, resulting in leakage of blood. The endothelium exposed to flow reversal initiates endothelial and leukocyte activation. This activates the inflammatory response further.

The trigger for all these is an inflammatory pathology. Repeated inflammatory response brings in recurring damage to vein wall and the valves. Several inflammatory mediators are identified in this setting. They include vascular cell adhesion molecule I, intercellular adhesion molecule I, transforming growth factor beta, fibroblast growth factor beta, and vascular endothelial

growth factor. The inflammatory cascade is a self-reinforcing process and damages the valves and affects the remodeling of vein wall.

In *the microcirculation*, venous hypertension increases the hydrostatic pressure leading onto interstitial edema. Leukocyte adhesion to capillary endothelium is promoted by venous hypertension, initiating intense inflammatory response. The inflammation leads onto widening of the gaps between the endothelial cells. The capillary permeability increases facilitating escape of macromolecules and RBCs into the interstitial space. An alternative theory is that there is an active transportation of RBCs and macromolecules through transendothelial channels [43]. Two other contributory factors are lymphatic damage and dysfunction of local nerve endings. Changes in the large veins would in turn produce alterations in the microcirculation and development of microangiopathy [44, 45]. Vincent and his colleagues have reported that failure of microvalves in the third- to sixth-generation tributaries would produce dermal backflow and skin changes, even in the absence of proximal reflux. Presence of reflux in the large veins further aggravates the skin changes [27].

Changes in the skin and dermal tissues over the gaiter area are obvious and visible. The target organ in CVI is the skin and subcutaneous tissues of the gaiter area. Several theories are offered to explain the skin and subcutaneous tissue damages. The stasis theory, the arteriovenous fistula theory, and the fibrin cuff theory have all been negated [43, 46]. The white cell trapping theory was proposed by Coleridge Smith and colleagues [46, 47]. This theory suggests that circulating neutrophils are trapped in the venous microcirculation as a consequence to venous hypertension and dependency of the limbs. The sluggish circulation and hypoxia in turn activate the neutrophils. The activated neutrophils produce tissue damage. Leukocyte activation is a major factor in the pathophysiology of CVI. But neutrophils could not be demonstrated in the capillaries. Hence, the credibility of the Coleridge Smith hypothesis has been challenged.

Pappas and colleagues have extensively reported on the venous microcirculation and endothelial cell characteristics [43, 48]. The dermal endothelial cells in patients with CVI were found to be normal on electron microscopic studies. There were no gaps between the cells. Gaps between the endothelial cells were considered to be the reason for escape of fluid and macromolecules leading onto tissue edema. These workers postulated that there is a transendothelial transportation of macromolecules. The macromolecules and red cells stimulate release of inflammatory mediators. Following this, leucocytes migrate to the interstitial space. Biopsy of gaiter areas in classes 4 and 5 patients revealed dominance of mast cells and macrophages. Lymphocytes, plasma cells, and neutrophils were not present in the perivascular space. Fibroblasts were observed in large numbers. The mast cell enzyme chymase is a potent activator of matrix metalloproteinases 1 and 3. The most characteristic finding observed in the dermal microcirculation in patients with CVI was the perivascular cuff and the accompanying collagen deposition. Originally, the perivascular cuff was thought to be due to fibrinogen extravasation and was erroneously referred to as "fibrin cuff." It is now realized that this cuff is formed by a ring of ECM proteins. These ECM protein cuffs can lead onto altered tissue remodeling and fibrosis. They also stimulate capillary angiogenesis. Pappas and team have suggested that endothelial cells of the dermal microcirculation are involved in the ECM cuff formation. These events are diagrammatically represented in Fig. 11.2a–c.

The cuff does not act as a diffusion barrier to oxygen and nutrients. Immunohistochemical studies have shown that the cuff "traps" TGF-β1 and α2-macroglobulins in its interstices. These trapped molecules are not available for the healing and regeneration of the dermal tissue resulting in altered tissue remodeling and fibrosis. This is known as the "trap hypothesis" [49].

Senescence of fibroblasts as a cause for ulceration was postulated by Hasan and colleagues based on the biopsy study of venous ulcers [50]. Failure to reepithelialize is the main reason for delayed healing of venous ulcers. These workers identified that dermal fibroblasts from venous ulcers are unresponsive to the action of transforming growth factor-β1. This could result from senescence of the cells. This defective response may cause faulty deposits of extracellular matrix which

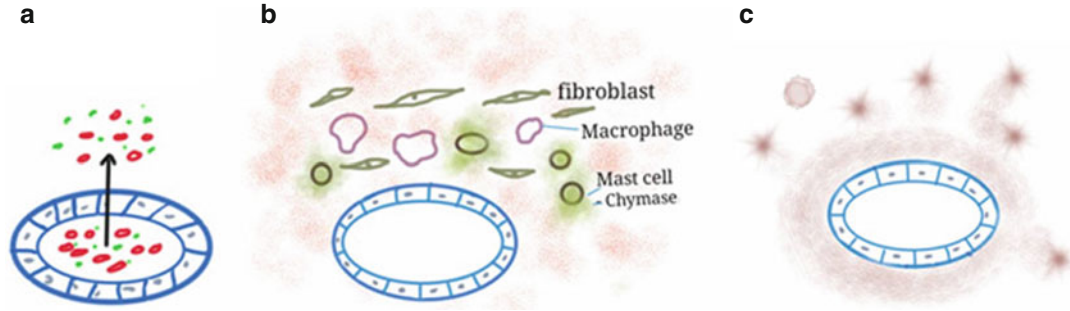

Fig. 11.2 Diagrammatic representation of molecular events. (**a**) Transendothelial migration of RBC and macromolecules. Endothelial cell gap normal. (**b**) Inflammation with presence of mast cell, macrophages, and fibroblasts. Mast cell chymase – activator of MMPS I and III. (**c**) ECM breakdown and formation of ECM cuff

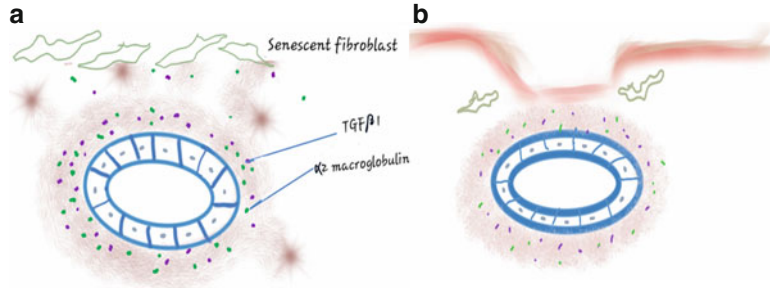

Fig. 11.3 Diagrammatic representation of molecular events. (**a**) Trapped TGF-β and α2-macroglobulin. Senescent fibroblasts. (**b**) Final outcome – chronic nonhealing ulcer

is needed for reepithelialization and wound healing. It was observed that basic fibroblast growth factor, epidermal growth factor, and interleukin-Iβ restored the growth potential of the senescent cells. This observation might imply a therapeutic potential for these factors in CVI [51] (Fig. 11.3a, b).

In conclusion, the microcirculatory events in CVI are a complex interplay of several factors. Venous hypertension is the trigger for these events. Alteration in ECM metabolism from overexpression of MMPs is a key factor along with diminished dermal fibroblast proliferation. Proper understanding of these cellular events can make way for the development of novel strategies for the prevention and treatment of venous ulcer.

Summary

Progression of a C2 clinical class of CVD to CVI is an unexplained and unpredictable event. A patient with varicose veins and leg ulcer is a common problem in clinical practice. The recurrent cycles of healing and breakdown of the ulcer impose considerable fiscal burden and social isolation for the patient. The basic hemodynamic defect in CVI is ambulatory venous hypertension.

Typical lesions of CVI are located over an area around the ankle, known as the gaiter area or ulcer-bearing area. There are specific anatomical reasons making this area vulnerable for such lesions.

Structural changes in the superficial and perforating veins in CVI are well known and easily correctable. Reflux in the deep veins due to valve failure is a finding constantly observed in a large number of patients along with reflux in superficial and perforator veins. Other areas demonstrating functional changes are the calf muscles, deep fascia of the leg, the ankle joint, and the lymphatic system.

A complex cascade of molecular events resulting from phlebitis has been identified. This is initiated by venous hypertension. The molecular events involve the large veins and the capillaries. The final target organ for these is the dermal tissue. A significant defect identified is an imbalance between MMPs and TIMPs.

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