

## Review Article

# Venous ulcers of the lower limb: Where do we stand?

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### ABSTRACT

Venous ulcers are the most common ulcers of the lower limb. It has a high morbidity and results in economic strain both at a personal and at a state level. Chronic venous hypertension either due to primary or secondary venous disease with perforator paucity, destruction or incompetence resulting in reflux is the underlying pathology, but inflammatory reactions mediated through leucocytes, platelet adhesion, formation of pericapillary fibrin cuff, growth factors and macromolecules trapped in tissue result in tissue hypoxia, cell death and ulceration. Duplex scan with colour flow is the most useful investigation for venous disease supplying information about patency, reflux, effects of proximal and distal compression, Valsalva maneuver and effects of muscle contraction. Most venous disease can be managed conservatively by leg elevation and compression bandaging. Drugs of proven benefit in venous disease are pentoxifylline and aspirin, but they work best in conjunction with compression therapy. Once ulceration is chronic or the patient does not respond to or cannot maintain conservative regime, surgical intervention treating the underlying venous hypertension and cover for the ulcer is necessary. The different modalities like sclerotherapy, ligation and stripping of superficial varicose veins, endoscopic subfascial perforator ligation, endovenous laser or radiofrequency ablation have similar long-term results, although short-term recovery is best with radiofrequency and foam sclerotherapy. For deep venous reflux, surgical modalities include repair of incompetent venous valves or transplant or transposition of a competent vein segment with normal valves to replace a post-thrombotic destroyed portion of the deep vein.

### KEY WORDS

Compression therapy; surgery on veins; venous hypertension; venous ulcers

In the course of a lifetime, almost 10% of the population will develop a chronic wound, with a wound-related mortality rate of 2.5%.<sup>[1]</sup> Of these, underlying venous pathology is the most common aetiology of lower extremity ulceration.<sup>[2]</sup> Even in the 21<sup>st</sup> century, studies

revealed the following effects of ulceration: pain, itching, altered appearance, loss of sleep, functional limitations, social isolation, depression and disappointment with treatment.<sup>[3,4]</sup> In 2011, an integrative review of previous studies on quality of life in patients with venous ulcers was published, which confirmed the negative impact of the disease on health-related quality of life.<sup>[5]</sup>

Venous ulcers are the result of breakdown of skin due to failure of preventing the consequence of chronic venous insufficiency. The disease has been known for more than 3.5 millennia, with wound care centers established as early as 1500 BC. Unfortunately, still today, it is a very

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poorly managed clinical condition by most physicians despite acquiring a great deal of knowledge about the pathogenesis and treatment for venous ulcerations.<sup>[6]</sup>

There is no available statistics related to the incidence of venous ulcers in India. But, an epidemiologic study on railway workers in 1972 found the incidence of varicose veins to be significantly higher in South Indians than in their northern counterparts.<sup>[7]</sup>

The morbidity of the disease, inadequate management, necessary logistic support and prolonged continuous care makes this disease a financial burden both at a personal and at the Government level. In the US, 80% of the lower extremity ulcers are venous ulcers, and the financial burden is \$2 billion per year.<sup>[8,9]</sup> Venous leg ulceration alone has been estimated to cost the NHS £400 m a year in the United Kingdom.<sup>[10]</sup> Studies in Germany calculated the mean total cost of a venous ulcer per patient per year to be €9569 (€8658-92% direct costs and €911-8% indirect costs).<sup>[11]</sup>

## ANATOMY AND PATHOPHYSIOLOGY

Venous return of the leg is dependent on two systems: deep and superficial, connected by perforator veins. Nomenclature of “deep” and “superficial” signifies their anatomic situations, either deep or superficial to the muscular fascia. There are unidirectional valves guiding the venous flow towards the heart. The deep system also includes the venous sinuses within, mainly, the soleus and, to a lesser extent, the gastrocnemii muscles. There are innumerable perforators between ankle and groin. They may be direct, draining to the axial deep veins (e.g., tibial, peroneal, popliteal, femoral) or indirect, draining to the venous sinuses in muscles. Powerful muscular contraction drives the blood within the venous sinuses as well as the deep system of the veins towards the heart. The superficial venous system empties into the deep systems via the perforators both at the junction of the deep and superficial systems and throughout the lower limb. However, in the feet, the flow is from the deep to the superficial system. Therefore, any derangement in the unidirectional venous flow towards the heart will affect the ankle region the most. Communicating veins are those connecting the veins within the same system, i.e. deep to deep, e.g. between the vena comitantes around the arteries, or superficial to superficial. The universal structure in venous system is venous valve - a thin fold of

endothelium supported by connective tissue. They remain open during supine position. As soon as a person stands up, there is a temporary retrograde flow for about 0.5 s, which is normal. Thereafter, the valves close, converting the entire venous system into segments of blood columns.<sup>[12,13]</sup> The deep venous systems empty due to muscular actions in feet, calf and thigh, and the blood from the superficial system passes on to them guided by perforators and the intact valves. Approximately 90% of the venous drainage in lower limbs is through the deep system.<sup>[14]</sup>

There are usually two main saphenous tributaries in the leg, an anterior branch and the posterior arch vein, which begins behind the medial malleolus and joins the great saphenous vein just distal to the knee. The posterior arch vein drains a network of medial ankle veins<sup>[15]</sup> and is important in that the posterior tibial perforators join this vein rather than the main trunk of the great saphenous vein. There are two main tributaries in the thigh with an important perforator in the adductor canal. The small saphenous vein usually drains in the popliteal vein but communications exist with the great saphenous system, and its terminations are variable.<sup>[16,17]</sup> In addition, there is a system that becomes important only under pathological conditions. Included in these are lateral superficial veins of the leg, which are remnants of the embryonic vena marginalis lateralis, the sciatic drainage system from the posterior thigh to the internal iliac system, the lateral subdermic system draining toward the femoral and inferior gluteal veins, the obturator veins and alternative venous pathways along the round ligament.<sup>[18]</sup>

The aetiological factors resulting in disturbance in venous return from the lower limb are:

### Primary venous disease

The aetiology of the functional, biochemical and structural changes associated with varicose veins remains unclear. Proposed mechanisms have included hypoxia-mediated endothelial changes,<sup>[19]</sup> cell cycle dysfunction with inhibition of programmed cell death,<sup>[20]</sup> changes in enzyme activity<sup>[21]</sup> and underlying defects in venous tone.<sup>[22,23]</sup> These ultimately result in loss of venous contractility and tone of veins, leading to dilatation and stretch. Valvular incompetence is a secondary phenomenon.<sup>[24]</sup>

### Secondary venous disease

Obstruction in the deep system is either due to thrombosis or destruction due injury. Post-thrombotic recanalisation process does not always destroy the valves, which, in

majority of the patients, are protected by fibrinolytic activity in their vicinity.<sup>[25-27]</sup> Yet, in about 10% of the patients, this mechanism fails and valves are destroyed. In secondary venous disease, both obstruction and reflux involving all the systems of veins ultimately play their roles in development of ulcers.<sup>[25,26]</sup>

#### **Failure of the valves**

This may occur both in deep and superficial systems as well as perforators. There may be paucity in numbers, inherent weakness of valves, failure secondary to degenerative process or destruction of the valves by thrombotic process.

#### **Others**

Old age, obesity, asthenia, calf muscle dysfunction and prolonged dependent posture are contributory factors in poor circulation and excess load on the valves.

Any of the above will ultimately lead to chronic venous hypertension. The severity of chronic venous disease is related to the magnitude of venous hypertension, with 100% ulceration at pressures greater than 90 mmHg.<sup>[28]</sup> As long as compensation can occur, the circulation will be normal although at the cost of increased load in the perforating and the superficial systems, which will ultimately fail, resulting in superficial varicosities, oedema, diapedesis and presence of various macromolecules in the interstitium leading to inflammatory reactions. Ulceration results from inflammation and theories that have been proposed are:

1. Leukocytes repeatedly trapped in microcirculation as a result of venous dilatation and pooling start releasing proteolytic enzymes that destroys tissues. Investigations proved about 24% less clearance of leukocytes in patients with ulceration in comparison with the normal or even in patients with varicose veins without ulceration. The clearance improves with response to treatment.<sup>[29]</sup> Endothelial damage, platelet aggregation and intracellular oedema follow as a consequence and contribute to impaired wound healing.
2. Interepithelial pore widening, deposition of fibrin and other macromolecules in dermis trap growth factors thus rendering them unavailable for wound repair.<sup>[30]</sup> There is also an abnormality in the fibrinolytic system. Immunohistochemical examinations have shown the presence of S-100 positive cells with dendritic cell morphology in the intima and media of veins with varicosity and thrombophlebitis. These dendritic cells

are postulated to stimulate T lymphocytes in various immune responses and their co-localization indicate the role of inflammation in the aetiopathogenesis of venous ulcers.<sup>[31]</sup>

## **CLINICAL ETIOLOGICAL ANATOMICAL PATHOLOGICAL CLASSIFICATION**

Developed under the auspices of the American venous forum,<sup>[32]</sup> the clinical etiological anatomical pathological (CEAP) classification encompasses clinical (based on objective signs), aetiological (congenital, primary and secondary), anatomical (distribution of reflux and obstruction) and pathophysiological (related to reflux or obstruction) mechanisms of venous disease. The clinical portion includes seven categories from non-existent venous disease to ulceration.

- C0 No visible or palpable evidence of venous disease
- C1 Telangiectasia and/or reticular veins
- C2 Varicose veins
- C3 Oedema
- C4 Changes ascribed to venous disease: pigmentation, venous eczema, lipodermatosclerosis
- C5 Skin changes as defined above with healed ulceration
- C6 Skin changes as defined above with active ulceration.

#### **Clinical features**

History should include events of deep venous thrombosis thrombophlebitis, trauma and different medications. Many of these patients are old and arterial disease, diabetes mellitus, neurotrophic ulceration should be excluded. Syndromic and non-syndromic vascular malformation, if any, should be looked for. Venous ulcers are shallow, usually around the ankle, with unhealthy granulation tissue and fibrinous exudate in the floor [Figure 1]. The base is schirrhous. Varicose veins are visible if not obscured by hyperpigmented, dermatosclerotic skin around the ulcers, which can be quite large. Sometimes, small cystic areas are seen, which are sites of impending rupture of skin [Figure 2]. Tenderness over the course of superficial veins indicate thrombophlebitis. Clinical examination to visualize perforator incompetence can be done by use of a rubber tourniquet at different levels in the lower limb. Important ones are junctional perforators like saphenofemoral and saphenopopliteal. Another important one in the thigh is at the adductor canal and in the calf. In addition, there are perforators connecting the posterior arch vein to the tibial system and ankle perforators and the small saphenous vein and tributaries



**Figure 1:** A typical chronic venous ulcer with granulation tissue and fibrinous exudate. Note the absence of necrotic material and hyperpigmented area surrounding the ulcer



**Figure 2:** Showing signs of bilateral venous hypertension with oedema and hyperpigmentation. The arrows point to cystic areas with very thin skin-impending ulceration likely

to the peroneal system. However, judgment of their incompetence can be difficult in lipodermatosclerosis. The use of tourniquet can also identify deep venous obstruction. The patient has a bursting sensation on walking due to obstruction in the superficial system by the tourniquet if the deep system is not patent.

### Investigations

Duplex scan with colour flow is the investigation of choice in venous pathology. It is non-invasive, gives valuable information regarding venous flow, thrombotic obstruction, patency and reflux, the effect of muscle contraction, proximal and distal compression and the Valsalva maneuver on each segment of the veins.<sup>[33]</sup>

Plethysmography and venous pressure data are important in determining the need for surgical bypass or valve replacement. Quantitative data on venous obstruction, calf muscle pump ejection fraction and reflux are provided by air plethysmography, whereas venous pressure studies assess the physiological importance of anatomic obstruction because the collaterals may or may not provide adequate compensation for an obstructed pathway.<sup>[34,35]</sup>

Ascending and descending venography are important only in candidates who are being considered for deep vein reconstruction.<sup>[36-38]</sup>

For long-standing ulcers, chronic osteomyelitis and malignant transformation should be kept in mind and, if necessary, appropriate investigations undertaken.

### Treatment

Treatment of venous ulceration should take into

consideration treatment of underlying venous hypertension, that of the ulcer and pharmacotherapy directed against inflammatory reactions.

## CONSERVATIVE MANAGEMENT

### Leg elevation

Any venous ulcer will heal if the patient takes rest with the lower limb elevated. Elevation above the heart level reduces oedema, improves venous drainage and microcirculation,<sup>[39]</sup> reduces stress on the valves and hastens ulcer healing. It has been shown to be beneficial if used for 30-min sessions, three or four times a day, which may not be practical in the present day settings. It is more effective when combined with compression therapy. In addition, life style changes in the form of weight reduction, exercise and avoiding prolonged standing help improve quality of life.

### Compression therapy

(Inelastic, elastic, intermittent pneumatic) is the standard of care and is associated with a decreased rate of ulcer recurrence. Although compression therapy is of proven benefit, the effect of intermittent pneumatic therapy is less evident. It reduces oedema and pain, improves venous circulation and enhances ulcer healing. Lifelong maintenance of compression therapy after ulcer healing reduces the rate of recurrence.<sup>[40-42]</sup> However, in the presence of eczematous dermatitis, obesity, pain and discharging ulcer, strict adherence to the regime of compression therapy becomes cumbersome.<sup>[43]</sup> Clinically significant arterial insufficiency and heart failure are contraindications to compression therapy.

Inelastic compression, although effective during

ambulation and muscle contraction, provides no resting pressure.<sup>[2]</sup> It fails to conform to the changes in size of the limb. Exemplified by Unna boot of yesteryears, it has practical difficulties of use due to foul-smelling discharge and need for frequent reapplications.<sup>[44]</sup>

Elastic compression sustains pressure during both ambulation and rest. In ulcerations, a pressure of around 35–40 mmHg is necessary. In the absence of ulcer, a pressure between 25 and 30 mmHg may suffice. Elastic bandages or stockings may be used.<sup>[45]</sup> The latter is more useful as it provides a graded pressure from below upwards, highest being at the ankle. It should be taken off at night and changed usually after 6 months as pressure is reduced by regular washing.<sup>[41]</sup>

Multilayered elastic bandages have proved to be more effective than single layered ones, but require skilled application and frequent change in the presence of discharge.<sup>[45-47]</sup>

#### **Medications**

Pentoxifylline (400 mg three-times daily) has been shown to be of additive beneficial effect to compression by dint of action on leucocyte metabolism, inhibition of platelet aggregation, reduction in viscosity of blood and consequent improvement in microcirculation.<sup>[48,49]</sup> But, its effect as monotherapy has not been shown to be cost effective.<sup>[2]</sup>

Aspirin (300 mg daily) is effective when used with compression therapy. It acts by reducing platelet adhesion.<sup>[50]</sup>

Intravenously administered iloprost may be beneficial through vasodilatation and its effect on platelet aggregation, but supporting data are limited and it is expensive.<sup>[49]</sup>

Oral zinc, despite having an anti-inflammatory effect, has not been shown to be useful.<sup>[51]</sup>

Micronised purified flavanoid fraction-Daflon 500 mg and prostaglandin E1 analogue-are used due to their action on leucocyte metabolism. These drugs are most effective when used in conjunction with compression.<sup>[52]</sup>

- a. Antibiotics are used in case of suspected cellulitis, and its routine use is not recommended.

#### **Mechanical**

Negative pressure wound therapy has been shown to

reduce the size of ulcers of various aetiologies. But, available data are insufficient to support its use in venous ulcers.<sup>[53]</sup> Moreover, it interferes with compression therapy and thus limits its use in venous ulcers.<sup>[54]</sup>

#### **Hyperbaric oxygen therapy**

It has potential antibacterial and anti-inflammatory effects that have been found to be useful in diabetic foot ulcers, but proof of its benefits in venous ulcers is lacking.<sup>[55]</sup>

#### **Dressings**

A wide variety of dressings are in use, including hydrocolloids, foams, hydrogels, pastes and simple non-adherent dressings. There is no evidence to prove superiority of one above the other and, therefore, the choice is based on available resources, personnel and individual preferences.<sup>[56]</sup>

#### **Surgical management**

Surgical management is indicated for ulcers that are large, of prolonged duration<sup>[57]</sup> or not responsive to conservative measures, including pharmacotherapy.<sup>[58]</sup> Although more research is needed regarding the comparative efficacy of various surgical approaches, options include debridement, human skin grafting and surgery for venous insufficiency, which is associated with a reduced rate of ulcer recurrence and may be helpful for severe or refractory cases. Artificial skin grafting with human skin equivalent may be effective when used with compression therapy, but concerns regarding infection transmission still remain.

#### **Debridement**

Debridement is the first step in the treatment of any wound or ulcer. This may be sharp and surgical, mechanical, autolytic, enzymatic or biological (larvae).<sup>[59-62]</sup> Many a times, morbidity and logistics come in the way of surgical debridement. In such situations, autolysis and subsequent mechanical debridement takes place due to regular lavage and change of dressings. Enzymatic preparations help in removal of necrotic tissue, but the process is slow and not practical for large ulcers. Usually, venous ulcers cause very little necrotic tissue and, in its presence, other causes like arterial insufficiency should be looked for.<sup>[49]</sup>

#### **Ulcer**

Treatment for ulcer is not different from any other ulcer. Split-thickness skin grafts, full-thickness skin grafts, local flaps [usually perforator based-Figure 3] and microvascular flaps all are suitable as cover provided the



**Figure 3:** (a) Recurrent venous ulcer in an elderly lady treated earlier with ligation of incompetent perforators and skin grafting for the ulcer. (b) The same patient with peroneal artery perforator-based flap for cover of the recurrent ulcer-2 years follow-up. Note the longitudinal scar for operation ligating the perforators of posterior arch vein

underlying pathology is dealt with. Sufficient evidence for efficacy of skin grafting alone for treatment of venous ulcers is lacking in the literature.<sup>[63]</sup>

### Underlying venous pathology

Surgical treatment aimed at correction of venous reflux should logically attack the sites of leakage, i.e. junctions of superficial and deep veins-the saphenofemoral and saphenopopliteal junctions as well as the incompetent perforator veins, particularly in the leg and sometimes also in the thigh. The tributaries of the great saphenous veins in the groin must also be ligated in order to prevent varicosity in them and in others through their connections in the future. Incompetent varicose veins have attenuated walls and act as venous lakes, creating peripheral blood pool. Their ablation helps improve venous circulation.

When the deep venous system is involved, there are three categories: (1) when there is a primary venous disease with valvular incompetence, (2) when there is a post-thrombotic destruction of valves or segments of deep veins, i.e. secondary venous disease and (3) a combination of both. In order to correct the failure of venous valves, direct surgery on them to prevent reflux was performed in cases of primary valvular disease. When there was total destruction of the valves in a small segment, either a bypass with grafts containing competent valves or transposition of an adjacent competent venous segment was carried out.

Any of the above, but usually in combination, is aimed at correction of underlying venous reflux, and this is more effective than compression therapy alone.<sup>[43,49, 64-66]</sup>

## TECHNIQUES

### Conventional surgery

Conventional surgery consists of saphenofemoral/saphenopopliteal flush ligation, disconnection of major tributaries, stripping/avulsion of varicose veins and perforator ligation through long incisions.<sup>[67,68]</sup> This surgery aims at only the superficial venous system.

### Subfascial endoscopic perforator ligation

Standard laparoscopic equipment with two 10-mm ports are used to ligate the incompetent perforator veins. Carbon dioxide at a pressure of 30 mmHg is used to insufflate the subfascial space to facilitate dissection and a pneumatic tourniquet is used in the thigh to obtain a bloodless field. This reduces morbidity and avoids the technical difficulties of working in lipodermatosclerotic tissue.<sup>[69,70]</sup>

### Sclerotherapy

Sodium tetradecylsulphate, polydocanol and 20% hypertonic saline are used to intentionally induce chemical phlebitis at the site of reflux and varicosities. Compression is to be ensured immediately after the injection, and this is an essential part for obliteration of the pathological vein. Mixing of sclerosant with air or carbon dioxide in various ratios to form a foam increases the efficacy of sclerotherapy. The use of ultrasound probe to track the needle and guide to the appropriate site of injection, and even track the dispersion of foam, is a further development in sclerotherapy. Sclerotherapy, although popular as an out patient department procedure, is effective for only small varicosities and localized form of the disease.<sup>[71]</sup>

### Radiofrequency ablation

Basically, this consists of delivery of infrared energy to the vein walls by directly heating the catheter tip with radiofrequency energy. Currently available equipment can monitor the core temperature of the catheter tip to about 120°C. Heat delivered to the vein wall causes shrinkage, and the catheter is withdrawn gradually until the entire vein is treated. This is performed in 7-cm segments. Advanced technology has ensured destruction, specifically of the vein wall, without carbonization or destruction of the surrounding tissue.<sup>[72]</sup>

### Endovenous laser surgery

Under perivascular infiltration of dilute local anesthesia, laser fibre is inserted in the great or small saphenous veins through a small puncture and under ultrasonic guidance advanced to the groin or knee crease. The laser is activated while it is withdrawn, resulting in obliteration of the vein.<sup>[73]</sup>

In a randomized trial comparing four modalities of treatments of great saphenous venous reflux viz. endovenous laser ablation, radiofrequency ablation, ultrasound-guided foam sclerotherapy and surgical stripping, technical failure was highest after sclerotherapy. The end point in this study however was ablation of great saphenous vein. Short-term recovery was best in the radiofrequency and foam sclerotherapy groups, but 1-year results were similar in each group.<sup>[71]</sup>

### Surgery for deep venous reflux

Surgery for deep venous insufficiency is a more difficult proposition. Here, there are two categories each with two subcategories of surgical procedure: (1) primary valve failure and (2) Secondary valve failure as a result of post-thrombotic destruction.

For primary valve failure, the attempted procedures are either intraluminal repair of valves or extraluminal support of the valve. Intraluminal repair consisted of tightening by sutures at the commissural level and, thereby, re-establishment of competence of the failed valve. Extraluminal support was provided by tightening of the vein wall externally at the site of the valve cusps without entering its lumen. The results however were better in the former.

For destroyed valves, either a segment of vein with normal valves is transplanted for the diseased segment or an adjacent normal vein is transposed in the diseased

segment. Long-term results reported in the literature in respect of ulcer recurrence after this procedure have been equivocal.<sup>[66,75,76]</sup>

### CONCLUSION

Venous ulcers are the most common of all leg ulcers, with high morbidity and strain on economic resources, and have a negative impact on quality of life.<sup>[3,4]</sup> It is unfortunate that many a times it is not properly diagnosed and, unnecessarily, expensive treatment is undertaken. Conservative management with leg elevation and compression therapy is effective and is the mainstay of therapy, particularly in the elderly and infirm not suitable for surgery. Dressings are dictated by economic and logistic factors and also preference of the treating physicians. No particular dressing material has been found to be superior to the others. Ulcers of prolonged duration not responding to conservative measures or patients who, for life style reasons, are unable to undertake it, will require surgery. The surgical procedures are directed at prevention of venous reflux at various levels and ablation of varicose veins followed by cover of the ulcers. However, compression therapy needs to be continued.

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