Venous Leg Ulcers

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In 1837, Piorry, a French professor of medicine stated, "It is rather difficult to understand why the investigation of veins has been passed over almost in silence, while such a great diagnostic value has been attached to the investigation of arteries." Even today, our understanding of venous disease pales in comparison to our understanding of arterial disease. This is despite the fact that millions of Americans are afflicted with chronic venous insufficiency and hundreds of thousands suffer from debilitating lower extremity venous ulcers. A better understanding of the pathophysiology of venous disease is necessary to provide appropriate and efficient medical care for patients suffering from lower extremity venous ulcerations.

Venous ulcers are the most severe and debilitating sequela of chronic venous insufficiency (CVI) and venous hypertension (HTN). They account for nearly 80% of all lower extremity ulcers, with an overall prevalence of approximately 1% to 2%.[1-8] It is estimated that more than 500,000 individuals in the U.S. suffer from an active leg ulcer at any given time.[1,6] The estimated medical cost of caring for patients with venous ulcers exceeds $1.8 billion a year.[3] Approximately 35% of patients afflicted with CVI will develop a venous ulcer before the age of 40 and nearly two thirds before the age of 65.[3,4] The majority of these patients are otherwise healthy individuals suffering from chronic wounds during the most productive period of their lives. Therefore, it is not unexpected that the financial burden of lost work and productivity exceeds the medical cost required to care for these patients.[3] Despite the prevalence of venous ulcers and the resulting financial burden, venous ulcers are often neglected and managed inappropriately. The purpose of this article is to review the pathophysiology, clinical presentation, and treatment of lower extremity venous ulcers.

Pathophysiology

The lower extremity calf-muscle pump, also known as the peripheral heart, is the body's primary mechanism for returning blood from the legs back to the heart.[2] The calf-muscle pump consists of the calf muscles, the deep-venous compartment, the superficial venous compartment, perforating veins, and an outflow tract (popliteal vein).[2] Dysfunction of any of the calf-muscle pump components may result in elevated venous pressure or venous HTN. Venous HTN is therefore caused by one or more of the following pathophysiologic mechanisms: (1) deep-vein obstruction (ie, thrombosis), (2) deep, perforating, or superficial vein valvular insufficiency (acquired or congenital), and (3) neuromuscular dysfunction.[2,3] In the setting of venous HTN, elevated pressure is transmitted to the subcutaneous tissues, causing microvascular damage and subsequent ulcer formation.[5] Although there is no consensus on the specific pathogenic steps leading from venous HTN to venous ulceration, several hypotheses have been proposed.[1-3,9-10]

In 1982, Browse and Burnand proposed the pericapillary fibrin cuff hypothesis.[1-5] This theory suggests that sustained venous HTN causes capillary distension and leakage of fibrinogen into the subcutaneous tissues.[1,3] Once in the extracellular space, fibrinogen polymerizes, forming pericapillary fibrin cuffs that act as a physical barrier to the diffusion of oxygen and nutrients into the soft tissues, causing cell death and tissue ulceration.[3] Although these pericapillary fibrin cuffs have been detected by direct immunofluorescence, they are discontinuous, shedding doubt on, but not completely excluding, their role as a physical barrier to small molecules like oxygen and other nutrients.[1-3]

In 1992, Falanga and Eaglstein proposed the growth-factor trap hypothesis. This theory posits that venous HTN causes capillary distention and leakage of fibrinogen and other macromolecules into the dermis.[3,6] These macromolecules trap growth factors and matrix proteins, making them unavailable for maintenance of tissue integrity and repair, resulting in ulcer formation.

Another theory proposed by Coleridge–Smith et al. and Cheatle et al. is the white cell trapping hypothesis. This theory describes a reduction of capillary blood flow in the setting of venous HTN. This reduction in blood flow causes accumulation and trapping of white cells within capillaries creating a physical barrier to oxygen, leading to local tissue ischemia.[1-3,8-11] Furthermore, activation of trapped white cells release proteolytic enzymes, free radicals, and cytokines into the surrounding tissues, resulting in chronic inflammation, tissue damage, and tissue ulceration.[1-3,8-11] The white cell trapping hypothesis is currently the most widely accepted theory explaining the pathogenesis of venous ulcer disease.[3,8] However, all three mechanisms likely contribute to ulcer formation since treatment options based on each theory have shown favorable outcomes in healing lower extremity venous ulcers.

Clinical Presentation

The clinical history of patients with CVI is usually characterized by a variety of symptoms. Symptoms of CVI include leg swelling, heaviness, aching, leg-tiredness, itching, and cramps.[3,4] These symptoms worsen at the end of the day after long periods of standing and improve with leg elevation.[3,4]

Venous ulcers are typically irregularly shaped, partial thick-

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ness wounds with well-defined borders (Fig 1).[1-8] They may be single or multiple and vary in size and a yellow-white exudate is frequently observed. Venous ulcers are most commonly located on the distal aspect of the lower leg, in the area known as the gaiter region.[11] Ulcers caused by greater saphenous vein insufficiency are usually located above the medial malleolus. Ulcers seen on the lateral aspect of the lower extremity are less common and are caused by short saphenous vein insufficiency.[12]

Examination of the lower extremity will demonstrate changes of CVI, supporting the diagnosis of leg ulceration as venous in origin. One of the earliest and most obvious signs of CVI are varicose veins. Dilated veins caudal to the medial malleolus are characteristic of CVI and are referred to as submalleolar venous flare.[3] A reddish-brown hyperpigmentation of the skin also may be present in patients with CVI. This skin discoloration is caused by extravasation of red blood cells into the dermis and subsequent hemosiderin deposition (Fig 2).[3] Atrophie blanche, described as smooth, white atrophic plaques of sclerosis mixed with telangiectases, is reported in up to 38% of patients with CVI.[3] Ulcerations of atrophie blanche lesions tend to be extremely painful and slow to heal.[3] Lipodermatosclerosis, another finding of CVI, frequently precedes venous ulcer formation. Acute and chronic forms of lipodermatosclerosis may be observed. The acute form is characterized by erythema, tenderness, and induration of the lower leg, which may be easily confused with cellulitis.[3] The two can be distinguished by a lack of fever, elevated white count, and improvement with antibiotic therapy in cases of acute lipodermatosclerosis.

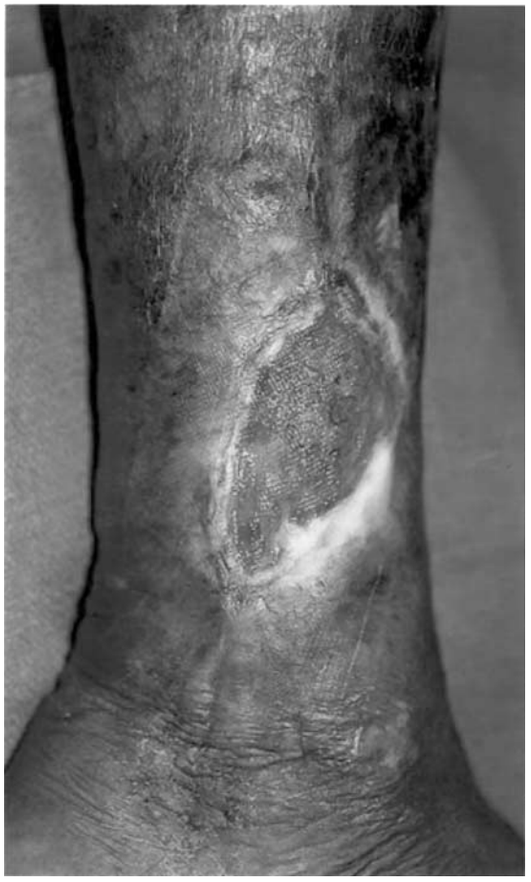

Fig 1. Lower extremity venous ulcer located above the medial malleolus. (Reprinted from Chronic venous insufficiency and venous leg ulceration, Valencia et al, 44:401-421, 2001 with permission from *American Academy of Dermatology*.)

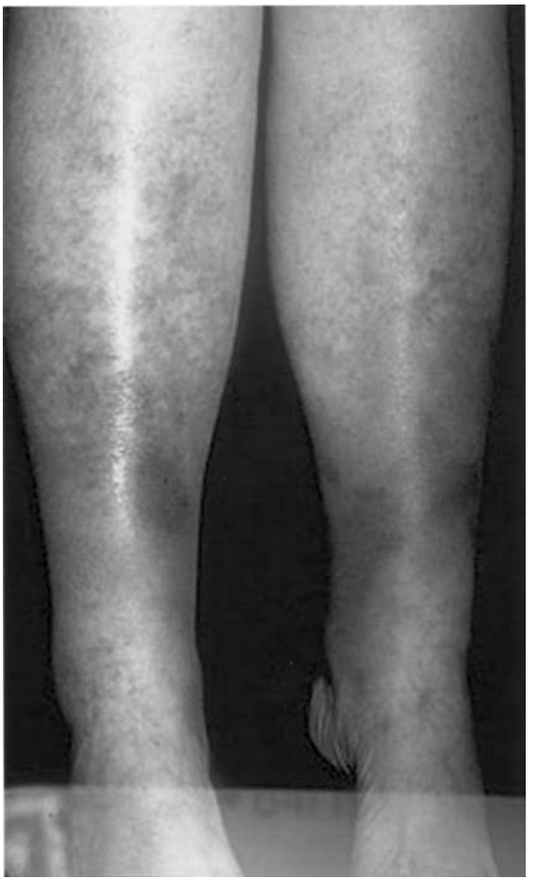

Fig 2. Hyperpigmentation of the skin caused by long-standing venous hypertension. (Reprinted from Chronic venous insufficiency and venous leg ulceration, Valencia et al, 44: 401-421, 2001 with permission from *American Academy of Dermatology*.)

Chronic lipodermatosclerosis is characterized by severe induration and fibrosis of the entire lower third of the leg, resulting in an "inverted champagne bottle" appearance (Fig 3).[3,13] Skin changes are typically restricted to the medial aspect of the lower leg and are sharply demarcated from normal adjacent skin.[3] Skin discoloration and atrophy of the soft tissues are common associated findings of chronic lipodermatosclerosis.

Differential Diagnosis

Although most lower extremity ulcers are venous in origin, other etiologies need to be considered in the differential diagnosis. The two most common causes of lower extremity ulceration after venous disease are arterial insufficiency and neuropathic ulcers.[14]

Arterial insufficiency ulcers are typically round, with sharply demarcated borders and a fibrous yellow base or necrotic eschar. They are found usually on the anterior or lateral aspect of the leg or ankle. Findings such as hair loss, shiny atrophic skin, cool feet, and weak or absent distal pulses support the diagnosis of arterial insufficiency as the cause of lower extremity ulceration.[3,14] These patients commonly will have abnormally low ankle/brachial indices (ABI < 0.5) and complain of claudication and/or rest pain. It is important to distinguish between peripheral vascular disease and venous disease because therapy for venous ulcers may worsen arterial insufficiency and possibly cause limb ischemia.

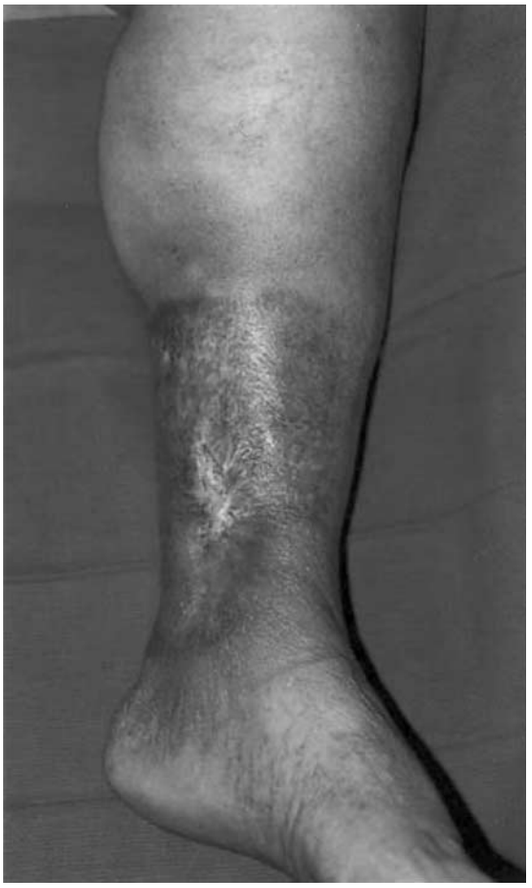

Fig 3. "Inverted champagne bottle" appearance of the lower extremity, a finding characteristic of chronic lipodermatosclerosis. (Reprinted from Chronic venous insufficiency and venous leg ulceration, Valencia et al, 44:401-421, 2001 with permission from *American Academy of Dermatology*.)

Neuropathic ulcers are found at sites of pressure points (ie, heel, metatarsal heads, toes) and are surrounded usually by heavy callous formation.[3,14] These ulcers can be of variable depth, ranging from superficial wounds to wounds involving tendons and osseous structures. Most neuropathic ulcers occur in patients with diabetes mellitus, but this is not without exception. These patients will complain of numbness, paresthesias, burning, and loss of sensation.

Fortunately, with intact sensation, normal distal pulses, and an ABI $\geq$ 0.9, the likelihood that an ulcer is caused by venous disease is well above 90%.[15] Color duplex ultrasound may be used to corroborate physical findings and is considered the diagnostic test of choice for evaluating lower extremity venous disease.

Other less common etiologies of leg ulcerations include vasculitis, metabolic disorders, lymphatic obstruction, hematologic disorders (ie, sickle cell disease), infection, pyoderma gangrenosum, and neoplasm (ie, squamous cell carcinoma).[14]

Treatment

Patients with venous ulcers will require medical therapy and possibly surgical intervention to promote ulcer healing and prevent ulcer recurrence. However, there are a few lifestyle changes a patient can make to assist medical therapy. For instance, patients should maintain a normal weight and a healthy, well-balanced diet. They should partake in a daily exercise routine (ie, 30-minute walks, 3 to 4 times a day), and avoid extended periods of sitting and/or standing.[2] Patients should periodically elevate their legs above heart level throughout the day and raise the foot of their bed with 6" blocks at night.[2] And finally, patients should avoid smoking because this may interfere with ulcer healing.

Compression Therapy

Compression therapy, using bandages or hosiery, is the mainstay of treatment for venous leg ulceration.[2,16-21] Compression therapy increases venous blood flow, decreases pathologic reflux during ambulation, increases ejection volume with activation of the calf muscles, and increases tissue pressure favoring absorption of edema.

To heal venous ulcers, compression therapy should be performed in two consecutive treatment phases.[2,3] The first treatment phase is the decompression phase, which should take place at the time of an active leg ulcer. The goal of this phase is to reduce edema and promote wound healing. For the decompression phase, three types of compression may be utilized: (1) inelastic compression bandages, (2) multi-layered elastic bandages, and (3) mechanical compression using intermittent pneumatic compression boots. Mechanical compression is reserved for patients who are unable to ambulate and for those who fail to respond to standard compression therapy.[2]

Inelastic compression bandages provide limited pressure at rest, but high pressure with activity.[4] The prototype of the inelastic bandage is the Unna boot, a moist, zinc oxide-impregnated paste bandage that hardens to an inelastic form.[4] Unna boots require frequent reapplication because they do not accommodate for changes in leg volume as edema subsides, and they have limited absorptive capacity for highly exudative wounds.[4] Modified, less rigid Unna boots have similar properties as the traditional Unna boot and are referred to as inelastic short-stretch bandages.[2,4]

The multi-layered elastic bandage system is comprised of a cotton or wool layer for absorption of exudate, one or two elastic wraps, and a self-adherent wrap that maintains the bandage in place.[4] Multi-layered elastic bandages exert continuous pressure (40-45 mm Hg at the ankle) at rest and with activity.[4] They require less frequent reapplication than inelastic bandages because they have the ability to conform to the lower extremity better and have superior absorptive capacity for highly exudative wounds.[3] The disadvantage to multi-layered inelastic compression bandages is that they require a certain degree of expertise for adequate application.

For the second phase or maintenance phase, which occurs after wound healing, elastic graduated compression stockings are used to control venous HTN and prevent ulcer recurrence.[2] For patients with arterial insufficiency, compression therapy should be used with caution. If necessary, then compression bandages that exert limited pressure at rest (ie, inelastic compression bandages) may be utilized.[2] Compression therapy is contraindicated in patients with severe peripheral vascular disease since this may worsen arterial insufficiency resulting in ischemia of the lower extremity.[2,3] A minimum pressure of 30 to 40 mm Hg (Class II stockings) should be used in patients with prior venous ulceration.[5] Patients should be instructed to wear graduated compression stockings indefinitely to prevent ulcer recurrence.[3] A much higher incidence of ulcer recurrence

has been shown in patients who are noncompliant (97%) compared with those who comply with medical therapy (10%).[22]

Surgical Intervention

Surgical correction of superficial, perforating, or deep-venous disease may be necessary for ulcer healing. The goal of surgical intervention is to improve venous hemodynamics when conservative therapy has failed. Extensive diagnostic venous evaluation should be performed before surgery to elucidate the pathophysiologic features and anatomic location of venous disease.[23]

Surgical stripping or sclerosis of the greater or short saphenous veins with or without stab avulsion of varicosities are treatment options for superficial insufficiency.[23-26] In cases of isolated superficial vein reflux, which occurs in up to 57% of cases, approximately 90% of ulcers will heal after surgical intervention.[24,25] However, controversy does exist regarding the efficacy of superficial vein surgery when concomitant deep-venous reflux (up to 32% of cases) is present.[24,25] Researchers have reported a benefit to saphenous vein ablation when deep-venous reflux is present, whereas others disagree with this approach.[25,26] Percutaneous treatment of incompetent superficial veins using laser or radiofrequency ablation offers a minimally invasive alternative to surgical stripping and will likely play a significant role in the treatment of venous ulcer disease.

The surgical treatment of incompetent perforating veins has greatly improved with the advent of subfascial endoscopic perforator surgery (SEPS). However, controversy does exist regarding the efficacy of SEPS because of the lack of a well-designed prospective, randomized, multicenter trial. The North American SEPS registry (148 SEPS procedures) comprised of mostly retrospective data reported an ulcer recurrence rate of 28% at 2-year follow-up.[27] However, because of inconsistencies in the registry's patient population and adjunctive procedures performed (ie, saphenous vein ablation, ligation, and varicosity avulsion), the efficacy of the SEPS procedure is difficult to ascertain from this report. Smaller prospective studies have found promising results; however, additional research is necessary to further evaluate the efficacy of SEPS for treatment of venous ulcer disease.[28]

Deep-venous reconstruction by direct valve repair, vein valve transposition, or transplantation should be reserved for severe cases of deep-venous insufficiency unresponsive to conservative management.[2,23] Direct valve repair offers the best clinical results. When repaired valves remain competent, rapid healing of ulcers has been reported in as many as 93% of cases, with recurrent ulcers occurring in approximately 12% of patients.[23] Venous bypass surgery is reserved for a small percentage (3-5%) of patients with deep-venous obstruction that fail conservative management.[23]

Wound Care

Local wound care, including debridement, is standard for venous ulcers. There are several different methods of wound debridement, including autolytic, chemical, and mechanical debridement.[3] Autolytic debridement is performed by placing an occlusive dressing under a compression bandage. This provides a protective moist environment, which helps accelerate wound healing.[3] Chemical debridement using proteolytic enzymes promotes wound healing by removing necrotic debris and fostering formation of healthy granulation tissue. Application of proteolytic enzymes to venous ulcers presumably works by removing fibrin cuffs and trapped macromolecules associated with venous ulcer formation.[3,4] Mechanical debridement using surgical instruments, wet-to-dry dressings, hydrotherapy, irrigation, and dextranomers has been used, but clinical research has failed to show a therapeutic benefit.[3] In addition, mechanical therapy with surgical instruments may actually impede ulcer healing because healthy granulation tissue may be removed along with necrotic debris.

Adjunctive Therapy

Promising research has been performed on using topical and perilesional injection of granulocyte-macrophage colony stimulating factor to help heal venous ulcers. Granulocyte-macrophage colony stimulating factor affects several phases of wound healing, including homeostasis, inflammation, proliferation, and maturation.[4] Its efficacy in promoting ulcer healing has been proven in several research studies.[29-32] However, further research is needed to determine the optimal dose and the best route of administration.[4]

Systemic therapy with Trental (Pentoxifylline), a methylxanthine derivative used in conjunction with compression therapy, has been proven effective in promoting ulcer healing.[33-35] Its positive effect on wound healing can be attributed to its fibrinolytic properties, antithrombotic effects, and ability to decrease white-cell adhesion to vascular endothelium.[4,33-35]

Conclusion

Venous ulcers are chronic wounds that impose a substantial economic burden on our health care system and significant morbidity for patients suffering from venous ulcer disease. Compression is the mainstay of therapy for patients with venous ulcerations. Surgery or newer endovascular techniques may improve venous hemodynamics, thereby increasing the rate of ulcer healing in patients who fail conservative management.

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