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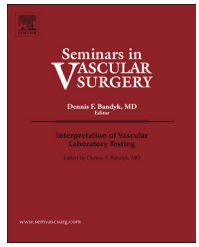

Pathogenesis of venous ulcer

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ABSTRACT

The underlying pathophysiology of venous ulceration is venous hypertension, which initiates a complex cascade of cellular humeral events that are then magnified by genetic factors. Hemodynamic abnormalities are features of primary and secondary chronic venous diseases that lead to disease progression. Through a sequence of events, some patients develop venous leg ulcers, if the process is not interrupted. The exact science of the pathophysiology of the progression of chronic venous disease to venous leg ulcers is still in its infancy, but the framework for future study has been established.

1. Pathophysiology of venous ulceration

Venus ulceration (Fig. 1) is the culmination of a cascade of complex cellular and humeral events that are magnified by genetic predisposition and initiated by venous hypertension [1]. This concept highlights two connected but distinct aspects of venous ulcer pathophysiology—an open wound leading to chronicity and pathologic hemodynamics. Hemodynamic abnormalities are essential features of primary and secondary chronic venous diseases (CVD). Reflux in deep veins can be present in both of these conditions, but obstruction is specific to post-thrombotic disease and nonthrombotic central vein compression commonly referred to as the May-Thurner lesion. Persistence of these hemodynamic abnormalities, namely, ambulatory venous hypertension, leads to progression of the disease and, through a cascade of events, some patients develop venous leg ulcers (VLUs) [1–4]. The process linking hemodynamic alteration to progression to ulceration includes changes in the microcirculation causing cellular and molecular mechanisms involving inflammation, proteolytic activity, and fibrosis [5–7].

In the case of post-thrombotic disease, inflammatory mechanisms are part of the initial thrombosis and persist through thrombus resolution. During thrombosis, thrombus resolution, and tissue response to venous hypertension, the vein wall and valves can be damaged by changes in activity and concentration of enzymes, adhesion molecules, vascular endothelial growth factor, matrix metalloproteinases (MMPs), inflammatory cytokines and interleukins, chemokines, plasmin, plasminogen activators, and inhibitors [8,9].

In patients with primary CVD, the vein wall and valves can be affected before development of hemodynamic abnormalities. Epidemiologic studies demonstrate that genetic and environmental factors play important roles in developing primary venous disease. Family history, female sex, pregnancy, estrogen levels, prolonged standing, sitting, and obesity are recognized as predisposing factors. Varicose veins appear early in the life of patients with Klippel-Trenaunay syndrome, CADASIL and FOXC2 gene mutations, desmulin dysregulation, and Ehlers-Danlos syndrome; indicating that genetic alteration is responsible for the development of primary CVD in some patients [5,10]. Other patients, however, do not have a clinically evident congenital disorder, therefore, a genetic link to their venous disease is often not recognized, but is important in the genesis and duration of their VLUs.

Whether the venous wall and valves are affected by primary CVD or the organization of thrombus resulting in venous obstruction, the subsequent hemodynamic changes

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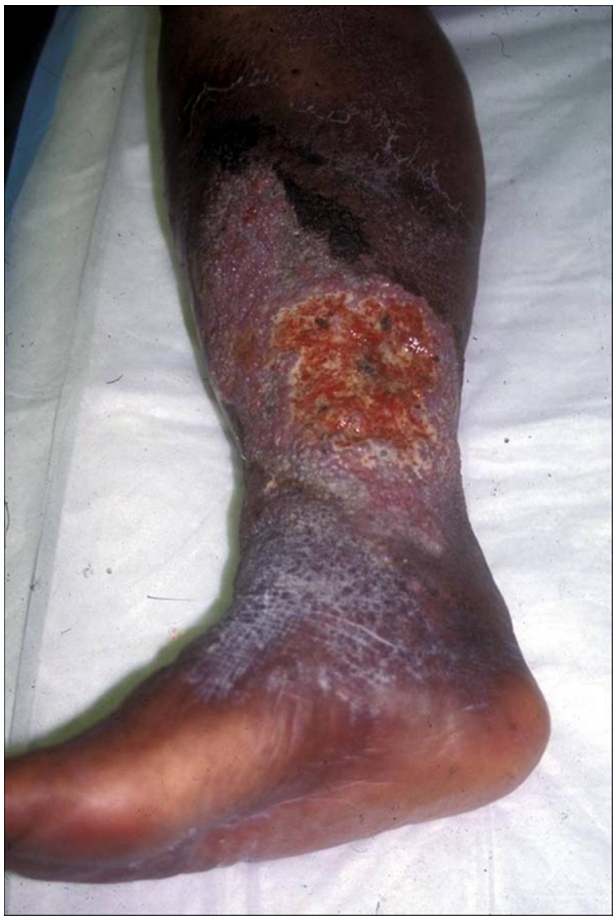

Fig. 1 – Patient with a long-standing, post thrombotic venous ulcer. Note the typical location, ulcer irregularity, hyperpigmentation of the skin of the lower leg and associated lipodermatosclerosis.

play an essential role in the progression of the earlier stages of CVD to VLU. The basic hemodynamic abnormalities in CVD are reflux, obstruction, and poor calf muscle pump function. The pathophysiologic interaction of these abnormalities is complex. Anatomic location and extent of reflux and obstruction and, in cases of post-thrombotic syndrome (PTS), a combination of reflux and obstruction in the same extremity, are among the factors determining the pathophysiology and severity of disease.

2. Venous physiology

The physiology of the lower extremity venous system is complex; however, it should be simplistically viewed as a combination of three major parameters: conductivity, capacitance, and directionality. Venous conductivity is the property of the venous system related to low resistance of main venous vessels, allowing transport of significant volumes of blood with relatively low energy expenditure. Venous capacitance is a mechanical property of the vein wall, which permits significant increases in vein diameter due to increased blood volume, without a commensurate increase in pressure. This is an important adaptive mechanism to variations of arterial inflow, cardiac output, and blood return. By the time the blood enters the venous system, its kinetic energy is depleted, and additional mechanisms are required to ensure the cardiopedal direction of blood flow. Three such mechanisms are the result of other physiological functions: respiration, cardiac contractions, and locomotion. Negative pressure in the chest resulting from respiratory movements and the pressure drop in the right atrium during the cardiac cycle generates a pressure gradient sufficient for moving blood from the lower extremity veins proximally. Contractions of calf muscles produced by ankle motion during normal locomotion act as a peripheral pump propelling venous blood proximally. A feature specific to the venous and lymphatic systems is the presence of one-way valves that, among other functions, prevent regurgitation of blood and lymphatic fluid.

Alteration in any of the three key parameters can result in venous dysfunction, including a decrease in conductivity, an increase in venous resistance, decrease of venous capacitance, incompetence of venous valves, and insufficiency of the calf muscle pump.

3. Valve incompetence

Multiple studies have demonstrated that patients with VLU have several distinct patterns of valvular incompetence. Isolated deep vein incompetence is uncommon, but when combined with perforator incompetence, it is associated with an 80% to 100% ulcer recurrence rate and prolonged ulcer healing [11,12]. Isolated great saphenous vein (GSV) incompetence is found in up to 25% to 50% of extremities with venous ulcers [13]. The Bonn Vein Study demonstrated a prevalence of GSV reflux in 57% of limbs with C5 to 6 CVD, and 29% in limbs with C2 CVD. The incidence of GSV reflux in the general population free of CVD was 2%. Adjusted odds ratio for the association of GSV reflux with severe chronic venous insufficiency was 7.02 (95% confidence interval, 4.52–10.91) for the GSV compared to 3.31 (95% confidence interval, 2.07–5.3) for deep vein reflux [14]. The combination of superficial and perforator incompetence is present in an additional 21% to 40% of extremities with VLU [15–17]. A similar prevalence was reported by the Edinburgh Vein Study [18].

Anatomic location is just part of the reflux pattern. The extent of reflux is equally, if not more, important. Axial reflux from groin to ankle is associated with the most severe CVD [19]. The Bonn Vein Study showed that when the deep reflux is axial, the risk of advanced CVD increases significantly (adjusted odds ratio = 11.25) compared to segmental deep reflux. The same relationships exist in individuals with GSV reflux. Natural history studies of CVD show similar relationships. An increase of the anatomic extent of reflux over time from segmental to axial is associated with increased severity of CVD [20,21].

The functional competence of venous valves determines the pathways of blood displaced from intramuscular veins and the effectiveness of the pump. Competent valves in perforating veins secure unidirectional flow from deep into the superficial veins. Competent valves in the superficial veins are necessary for further propagation of the flow into