Pathophysiology of Chronic Venous Disease and Venous Ulcers

Joseph D. Raffetto, MD[a,b,*]

KEYWORDS

• Chronic venous disease • Venous leg ulcers • Inflammation • Adhesion molecules • Endothelial dysfunction • Glycocalyx • Cytokines • Matrix metalloproteinases

KEY POINTS

- Venous reflux and obstruction leads to venous hypertension.
- Genetic predisposition and various candidate genes and their polymorphisms and environmental factors are important in the development of chronic venous disease.
- Inflammatory cells have a central role in the pathophysiology of chronic venous disease and venous leg ulcers.
- Changes in the glycocalyx and shear stress lead to dysfunctional endothelium and expression of adhesion molecules that attract leukocytes initiating events of inflammatory response.
- Cytokines and matrix metalloproteinases are expressed in chronic venous disease, particularly in venous leg ulcers, and are responsible for persistent impaired wound healing but also are necessary for wound closure.

INTRODUCTION

Chronic venous disease (CVD) is a debilitating condition that affects millions of individuals worldwide. The condition can result in varicose veins, or advance to severe skin changes and venous ulceration. Both reflux and obstruction account for the pathophysiology of CVD; however, reflux has a much higher prevalence in patients presenting with the different stages of CVD including venous leg ulcers (VLU), but obstruction has a higher rate of patients developing venous ulceration, and has a much more rapid progression of disease.[1–5] Whether reflux or obstruction is the cause for the patient's clinical presentation and symptomatology, both conditions lead to increased ambulatory venous pressure. Genetic and environmental factors influence predisposition to

The author has nothing to disclose.
[a] Harvard Medical School, VA Boston Healthcare System, Brigham and Women's Hospital, Boston, MA, USA; [b] VA Boston HCS, Surg 112, 1400 VFW Parkway, West Roxbury, MA 02132, USA
* VA Boston HCS, Surg 112, 1400 VFW Parkway, West Roxbury, MA 02132.
E-mail address: joseph.raffetto@med.va.gov

Surg Clin N Am 98 (2018) 337–347
https://doi.org/10.1016/j.suc.2017.11.002
0039-6109/18/Published by Elsevier Inc.

CVD and VLU. Inflammatory cells are activated on changes in shear stress and endothelial cell disruption. Matrix metalloproteinases (MMPs) are activated and changes in the structural components of the vein wall collagen and elastin occur, and extracellular matrix degradation resulting in CVD as seen in varicose veins, skin changes, and VLU. The fundamental basis for CVD and venous ulceration is inflammation within the venous circulation that is subjected to increased hydrostatic pressure, resulting in increased ambulatory venous pressure, increased inflammation within the vein wall and valve leaflet, and extravasation of inflammatory cells and molecules into the interstitium.[6–8] The inflammatory response involves leukocytes, in particular macrophages and monocytes, and T lymphocytes and mast cells, inflammatory modulators and chemokines, cytokine expression, growth factors, metalloproteinase activity, and many regulatory pathways that perpetuate inflammation and the resultant changes seen with CVD (**Fig. 1**).[9–14]

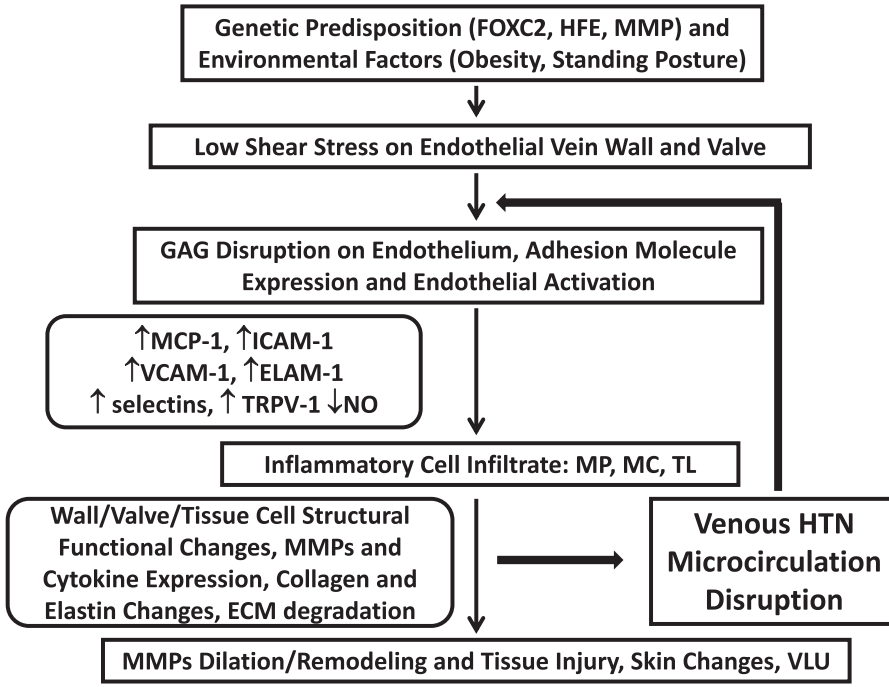

Fig. 1. Schematic flow diagram of chronic venous disease pathophysiology. Genetic and environmental factors predispose individuals to venous disease, changes in shear stress and endothelial integrity lead to adhesion molecule expression and leukocyte-endothelial activation, initiating an inflammatory response with expression of cytokines, chemokines, and matrix metalloproteinases. Changes in venous wall structure and valve function lead to venous dilation and insufficiency, venous hypertension, and disruption in the microcirculation. Persistent inflammatory state with matrix metalloproteinase and cytokine expression causes tissue damage and degradation resulting in skin changes and venous leg ulcer. ECM, extracellular matrix; ELAM-1, endothelial leukocyte adhesion molecule-1; FOXC2, forkhead box protein C2 gene; GAG, glycosaminoglycan; HFE, hemochromatosis gene; HTN, hypertension; ICAM-1, intercellular adhesion molecule-1; MC, mast cells; MCP-1, monocyte chemotactic protein-1; MP, macrophages; NO, nitric oxide; TL, T lymphocytes; TRPV-1, transient receptor potential vanilloid channels; VCAM-1, vascular cell adhesion molecule-1.