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Mechanism of disease: the inflammatory chain in chronic venous disorders and genetic screening for prevention of venous leg ulcers

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The inflammatory chain following venous outflow obstruction/reflux, and consequent microcirculatory overload, can be nowadays considered practically deciphered. Tissue drainage becomes insufficient because venous hypertension influences trans-mural pressure (TMP). Increased TMP determines expression of adhesion molecules on the endothelial cells, promotes red blood cells extra-vasation and either dermal hemosiderin deposits or iron laden-phagocites. Iron plays a role in the pathogenesis of venous leg ulcers: local iron overload may generate free radicals or activates a proteolytic hyperactivity of metalloproteinases (MMPs) or else down regulate tissue inhibitors of MMPs. These negative effects are particularly evident in carriers of the common HFE gene's mutations C282Y and H63D, because intracellular iron deposits of mutated macrophages have less stability than those of the wild type, inducing a significant oxidative stress. It has been proven that these mutations increase the risk of ulcers and advance the age of ulcer onset, respectively. The inflammatory iron-dependent chain in CVD paves the way to new therapeutic strategy including the deliberate induction of iron deficiency as a treatment modality for non healing and/or recurrent venous leg ulcers. In addition, relatives of ulcers patients, carriers of the HFE mutation, when affected by CVD could undergo to genetic screening followed by a prevention program of venous leg ulcers.

KEY WORDS: Inflammation - Chronic venous disease - Venous ulcers - Transmural pressure - Iron overload - Genetic screening.

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Impaired venous drainage of the lower extremities, mainly do to venous reflux or, sometimes, to venous outflow obstruction, determines a cascade of pathologic events clinically graded by the clinical class (C) of the CEAP classification of chronic venous disease (CVD).[1] A small, but significant, number of the affected patients will develop venous ulcers, whose overall prevalence in Western countries is between 1 and 2%.[2-10]

Historical background

Impaired venous drainage of the lower extremities, is a necessary but not sufficient element for explaining the progression of the disease to the point of skin lesion.

For such reason, in the past 20 years, a number of adjunctive factors have been investigated to understand the ethiology of venous ulceration, but none of them completely explains the entire process. In 1982, Browse and Burnand[11] observed a pericapillary fibrin deposition and speculated that cuffs act as barrier to oxigen diffusion and nutrientes, resulting in epidermal cell death. However, this deficit in nutrient