REVIEW ARTICLE

MECHANISMS OF DISEASE

Chronic Venous Disease

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CHRONIC VENOUS DISEASE OF THE LOWER LIMBS IS MANIFESTED BY A range of signs, the most obvious of which are varicose veins and venous ulcers. However, the signs also include edema, venous eczema, hyperpigmentation of skin of the ankle, atrophie blanche (white scar tissue), and lipodermatosclerosis (induration caused by fibrosis of the subcutaneous fat) (Fig. 1). Considerable progress has been made in understanding the mechanisms that underlie these diverse manifestations, in particular the role of inflammation. This article reviews these advances and places them in a clinical context.

Chronic venous disease can be graded according to the descriptive clinical, etiologic, anatomical, and pathophysiological (CEAP) classification, which provides an orderly framework for communication and decision making.[1,2] The clinical signs in the affected legs are categorized into seven classes designated C_0 to C_6 (Table 1). Leg symptoms associated with chronic venous disease include aching, heaviness, a sensation of swelling, and skin irritation; limbs categorized in any clinical class may be symptomatic (S) or asymptomatic (A). Chronic venous disease encompasses the full spectrum of signs and symptoms associated with classes $C_{0,s}$ to C_6, whereas the term "chronic venous insufficiency" is generally restricted to disease of greater severity (i.e., classes C_4 to C_6). Thus, varicose veins in the absence of skin changes are not indicative of chronic venous insufficiency.

THE SCALE OF THE PROBLEM

PREVALENCE

Chronic venous disease is extremely common, although the prevalence estimates vary. A cross-sectional study of a random sample of 1566 subjects 18 to 64 years of age from the general population in Edinburgh, Scotland,[3] found that telangiectases and reticular veins were each present in approximately 80 percent of men and 85 percent of women. Varicose veins were present in 40 percent of men and 16 percent of women, whereas ankle edema was present in 7 percent of men and 16 percent of women.[3] Active or healed venous leg ulcers occur in approximately 1 percent of the general population.[3,4]

Although not restricted to the elderly, the prevalence of chronic venous disease, especially leg ulcers, increases with age.[3-5] Most studies have shown that chronic venous disease is more prevalent among women, although in a recent study, the difference between sexes was small.[6] In the Framingham Study, the annual incidence of varicose veins was 2.6 percent among women and 1.9 percent among men,[7] and in contrast to the Edinburgh Vein Study, the prevalence of varicose veins was higher in men.[3,8] In the San Diego Population Study, chronic venous disease was more prevalent in populations of European origin than in blacks or Asians.[9] Risk factors for chronic venous disease include heredity, age, female sex, obesity

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Figure 1. Clinical Manifestations of Chronic Venous Disease.

Telangiectases (clinical, etiologic, anatomical, and pathophysiological [CEAP] class C_1) are shown in Panel A, varicose veins (CEAP class C_2) in Panel B, pigmentation (CEAP class C_4) in Panel C, and active ulceration (CEAP class C_6) in Panel D.

Table 1. Revised Clinical Classification of Chronic Venous Disease of the Leg.*

Class	Definition	Comments
C_0	No visible or palpable signs of venous disease	
C_1	Telangiectases, reticular veins, malleolar flare	Telangiectases defined by dilated intradermal venules <1 mm diameter Reticular veins defined by dilated, nonpalpable, sub-dermal veins ≤3 mm in diameter
C_2	Varicose veins	Dilated, palpable, subcutaneous veins generally >3 mm in diameter
C_3	Edema without skin changes	
C_4	Skin changes ascribed to venous disease	
C_{4A}		Pigmentation, venous eczema, or both
C_{4B}		Lipodermatosclerosis, atrophie blanche, or both
C_5	Skin changes with healed ulceration	
C_6	Skin changes with active ulceration	

* Adapted from Porter and Moneta[1] and Eklof et al.[2]

(especially in women), pregnancy, prolonged standing, and greater height.[4,8,10-12]

ECONOMIC IMPACT

The high prevalence of varicose veins and the chronicity of leg ulcers mean that chronic venous disease has a considerable impact on health care resources. In a population study in the United Kingdom, the median duration of ulceration was nine months, 20 percent of ulcers had not healed within two years, and 66 percent of patients had episodes of ulceration lasting longer than five years.[13] It has been estimated that venous ulcers cause the loss of approximately 2 million working days and incur treatment costs of approximately $3 billion per year in the United States.[14] Overall, chronic venous disease has been estimated to account for 1 to 3 percent of the total health care budgets in countries with developed health care systems.[4,15,16]

SYMPTOMS AND QUALITY OF LIFE

Symptoms traditionally ascribed to chronic venous disease include aching, heaviness, a feeling of swelling, cramps, itching, tingling, and restless legs. The proportion of patients presenting with any venous symptom increases with increasing CEAP class.[17] In an international study of 1422 patients with chronic venous disease, the overall score for symptom severity was significantly correlated with the CEAP clinical class, after controlling for age, sex, body-mass index, coexisting

conditions, and the duration of chronic venous disease.[18]

Chronic venous disease is associated with a reduced quality of life, particularly in relation to pain, physical function, and mobility. It is also associated with depression and social isolation.[19] Venous leg ulcers, the most severe manifestation of chronic venous disease, are usually painful[20] and affect the quality of life.[21] A large-scale study of 2404 patients using the generic Medical Outcomes Study 36-item Short-Form General Health Survey questionnaire found a significant association between the quality of life and the severity of venous disease.[22] Similarly, a correlation between the CEAP class and the quality of life has been found with the use of a disease-specific questionnaire.[18] The impairment associated with CEAP classes C_5 and C_6 has been likened to the impairment associated with heart failure.[23]

VENOUS HYPERTENSION

Despite the diversity of signs and symptoms associated with chronic venous disease, it seems likely that all are related to venous hypertension. In most cases, venous hypertension is caused by reflux through incompetent valves,[6,24] but other causes include venous outflow obstruction and failure of the calf-muscle pump owing to obesity or leg immobility. Reflux may occur in the superficial or deep venous system or in both. A review of 1153 cases of ulcerated legs with reflux found superficial reflux alone in 45 percent, deep reflux

alone in 12 percent, and both forms in 43 percent.[25] An analysis of cases of chronic venous disease indicated that primary valvular incompetence was present in 70 to 80 percent and a congenital anomaly in 1 to 3 percent; valvular incompetence was due to trauma or deep-vein thrombosis in 18 to 25 percent.[6,24]

Pressure in the veins of the leg is determined by two components: a hydrostatic component related to the weight of the column of blood from the right atrium to the foot and a hydrodynamic component related to pressures generated by contractions of the skeletal muscles of the leg and the pressure in the capillary network. Both components are profoundly influenced by the action of the venous valves. During standing without skeletal-muscle activity, venous pressures in the legs are determined by the hydrostatic component and capillary flow, and they may reach 80 to 90 mm Hg. Skeletal-muscle contractions, as during ambulation, transiently increase pressure within the deep leg veins. Competent venous valves ensure that venous blood flows toward the heart, thereby emptying the deep and superficial venous systems and reducing venous pressure, usually to less than 30 mm Hg (Fig. 2). Even very small leg movements can provide important pumping action. In the absence of competent valves, however, the decrease in venous pressure with leg movements is attenuated. If valves in the perforator veins are incompetent, the high pressures generated in the deep veins by calf-muscle contraction can be transmitted to the superficial system and to the microcirculation in skin. It seems likely, therefore, that the clinical signs of chronic venous disease stem from venous pressures in the leg that reach higher-than-normal levels and remain elevated for prolonged periods.

VALVE AND VEIN-WALL CHANGES IN CHRONIC VENOUS DISEASE

CHANGES IN VENOUS VALVES

Venous valve incompetence is central to the venous hypertension that appears to underlie most or all signs of chronic venous disease. Alterations in and damage to valves have been noted on examination with an angioscope, a fiberoptic catheter that allows clinicians to view the interior of a blood vessel. These changes include stretching, splitting, tearing, thinning, and adhesion of valve leaflets.[27] A reduction in the number of valves
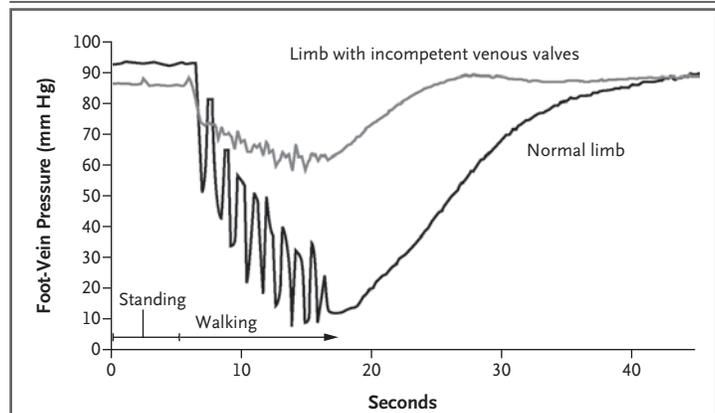
Figure 2. Action of the Musculovenous Pump in Lowering Venous Pressure in the Leg.

After prolonged standing, venous pressure in the foot is approximately 90 mm Hg in both a patient with incompetent venous valves and a person with a normal leg. During walking, the musculovenous pump rapidly lowers the venous pressure in the normal leg but is ineffective in the leg with valvular incompetence. (Reproduced from Coleridge Smith[26] with the permission of the publisher.)

per unit length has been observed in segments of saphenous veins from patients with chronic venous insufficiency.[28] An important step forward came when Ono et al.[29] found infiltration of valve leaflets and the venous wall by monocytes and macrophages in all vein specimens from patients with chronic venous disease and in no specimens from controls. Infiltration was associated with areas of endothelium that expressed intercellular adhesion molecule 1 (ICAM-1).[30]

STRUCTURAL CHANGES IN THE VEIN WALL

Histologic and ultrastructural studies of varicose saphenous veins have found hypertrophy of the vein wall with increased collagen content,[31] together with disruption of the orderly arrangements of smooth-muscle cells and elastin fibers.[32,33] Cultures of smooth-muscle cells from varicose saphenous veins have disturbed collagen synthesis, resulting in overproduction of collagen type I and reduced synthesis of collagen type III.[34] Because collagen type I is thought to confer rigidity and collagen type III to confer distensibility to tissues, such changes could contribute to the weakness and reduced elasticity of varicose veins.

A complicating factor is the heterogeneity of the varicose-vein wall; hypertrophic segments can alternate with thinner atrophic segments with fewer smooth-muscle cells and reduced extracellular matrix. Degradation of extracellular matrix

proteins is caused by an array of proteolytic enzymes, including matrix metalloproteinases (MMPs) and serine proteinases, which are produced by vascular cells and inflammatory cells such as macrophages.[35] MMPs are released as inactive proenzymes that are activated by other proteinases, including those produced by mast cells,[36,37] whereas tissue inhibitors of MMPs (TIMPs) reduce MMP activity. In varicose veins, ratios of TIMP-1 to MMP-2 and TIMP-2 to MMP-2 have been found to be 3.6 times and 2.1 times, respectively, those in veins of control subjects.[38] These altered ratios could favor the accumulation of extracellular matrix material in varicose veins.

Elevated levels of the cytokines transforming growth factor β_1 (TGF-β_1) and fibroblast growth factor β (FGF-β, also referred to as basic fibroblast growth factor) have also been found in the walls of varicose veins.[39] TGF-β_1 stimulates collagen and elastin synthesis and increases the expression of TIMPs,[40] whereas FGF-β is chemotactic and mitogenic for smooth-muscle cells.[41] These findings of changes in proteolytic enzymes and their inhibitors and cytokines could signal the beginning of an understanding of the mechanisms that cause hypertrophic changes in the vein wall.[42] Other changes have been found in varicose regions of saphenous veins, which contain increased numbers of mast cells.[43] Proteinases from mast cells can activate MMPs, which degrade extracellular matrix. With time, local differences in the balance of opposing synthetic and degradative processes could lead to hypertrophic and atrophic segments of the same vein.

ROLE OF PRESSURE AND SHEAR STRESS

THE ROLE OF ELEVATED PRESSURE

The acute effects of increased venous pressure have been studied in animal models. In rats, production of an arteriovenous fistula between the femoral artery and vein abruptly increased the pressure in the femoral vein to approximately 90 mm Hg.[43-45] Although the valves were stretched immediately by the increased pressure, reflux did not occur until at least two days later and then increased with time. After three weeks, the numbers of granulocytes, monocytes, macrophages, and lymphocytes were increased in the pressurized valves, and MMP-2 and MMP-9 levels were raised. Morphologic changes in the valves also occurred; there were reductions in leaflet height and width,

and some valves disappeared. These studies suggest that valves can tolerate high pressures for limited periods, but when there is prolonged pressure-induced inflammation, valve remodeling and loss and reflux occur.

When a rat mesenteric venule was experimentally occluded, the effects of increased pressure could be separated from the effects of reduced flow by comparing regions on either side of the occlusion; flow was essentially zero at both sites, but only the upstream site had high pressure.[46,47] Leukocyte rolling, adhesion, and migration, as well as microhemorrhage and parenchymal-cell death, were all increased at the high-pressure site.

THE ROLE OF SHEAR STRESS

Before considering the molecular mechanisms by which shear stress modulates endothelial and leukocyte behavior, we will summarize recent work on blood flow through venous valves. Venous valves are operated by pressure rather than by flow-driven devices, so that little or no reflux is needed to bring about complete closure of the valve.[48] The recently introduced technique of B-flow ultrasonography has allowed detailed investigation of patterns of blood flow and valve operation in situ.[49] Venous flow is normally pulsatile; venous valves open and close approximately 20 times per minute while a person is standing. When the valve leaflets are fully open, they do not touch the sinus wall (Fig. 3). Flow through the valve separates into a proximally directed jet and a vortical flow into the sinus pocket behind the valve cusp; the vortical flow prevents stasis in the pocket and ensures that all surfaces of the valve are exposed to shear stress. Valve closure occurs when the pressure caused by the vortical flow exceeds the pressure on the luminal side of the valve leaflet because of the proximally directed jet. Interestingly, foot movements, which increase the velocity of the jet, reduce the pressure on the luminal side of the valve leaflets and cause closure of the valve. Thus, minimal reflux occurs and endothelial surfaces are not generally exposed to reverse blood flow.
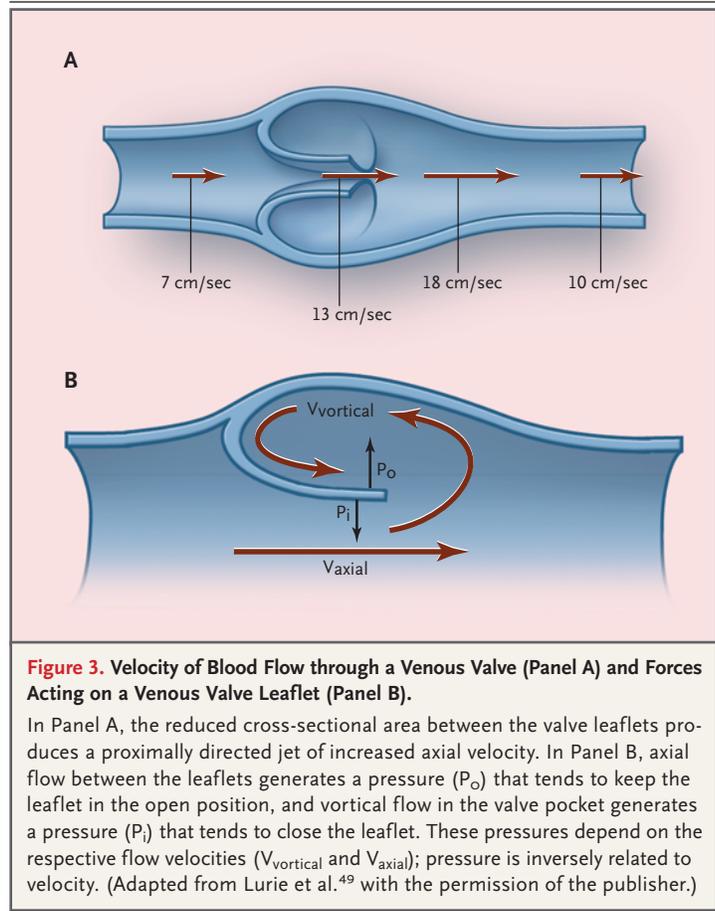
Shear stress is transduced in endothelial cells by several possible mechanisms and mediated by a complex network of signaling pathways[50,51] that can modify the expression of numerous genes.[52] An important theme of current research on the effects of shear stress is that pulsatile, laminar shear stress can promote the release of factors

that reduce inflammation and the formation of reactive free radicals. By contrast, low or zero shear stress, disturbed or even turbulent flow, and especially reversal of the direction of flow all promote an inflammatory and thrombotic phenotype (Fig. 4).[50,53-55] These processes operate in the venous and arterial systems, where they may underlie the observation that atherosclerotic lesions occur preferentially in regions of low or reversing shear stress.[56,57]

Leukocytes respond to fluid shear stress by the rapid retraction of pseudopods and the shedding of CD18 adhesion molecules; neutrophils attached to a glass surface round up and detach when exposed to shear stress.[58,59] The response to shear stress is suppressed by inflammatory mediators and enhanced by donors of nitric oxide.[60]
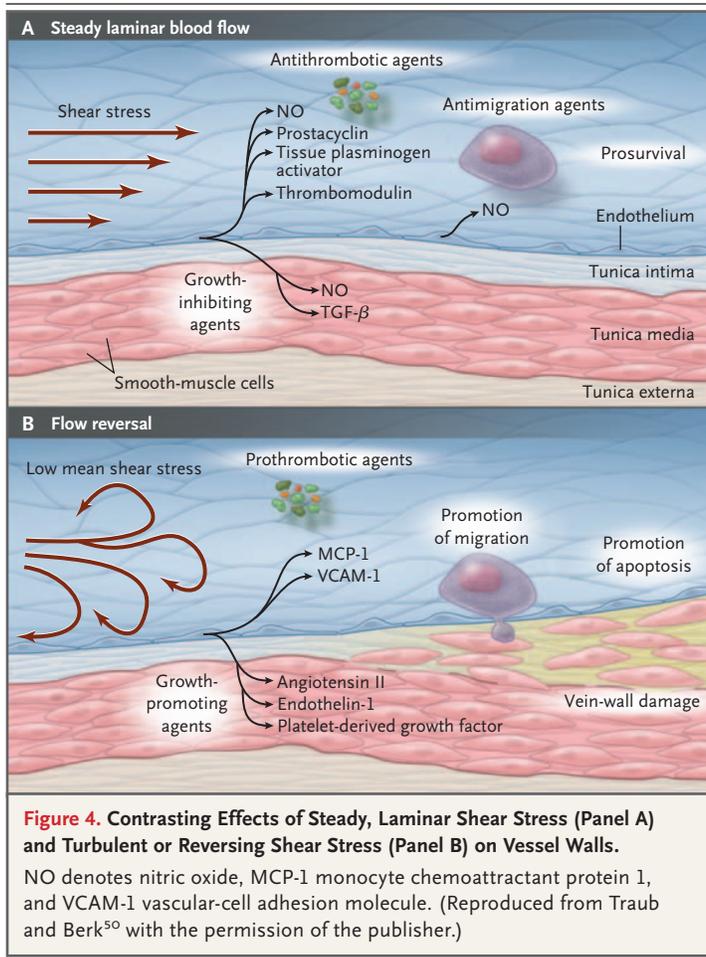
Several aspects of the inflammatory process include elements of positive feedback or amplification. For example, the endothelial glycocalyx is likely to have a profound influence on the transduction of shear stress by endothelial cells.[61] Nearly all of the mechanical stress caused by luminal flow is transferred to the glycocalyx; shear stress at the endothelial-cell surface itself is extremely small.[61] The glycocalyx may also mask cell adhesion molecules and prevent leukocyte adhesion.[62,63] However, inflammation can cause disruption or shedding of the glycocalyx,[64] which will alter shear stress responses and may promote further leukocyte adhesion.[63]

It is not known what initiates the inflammatory events in venous valves and walls. Altered shear stress may be important in several ways. Prolonged pooling of blood causes distention of lower limb veins and distortion of venous valves. Leakage through such valves exposes endothelial cells to flow reversal. Venous stasis, even in the absence of reflux, produces regions of low or zero shear stress, whereas subsequent structural changes and irregularities in vessel walls may induce regions of disturbed and even turbulent flow. All of these events can initiate and maintain inflammatory reactions. Overall, it appears that inflammatory processes involving leukocyte–endothelial interactions and triggered largely in response to abnormal venous flow are important in causing the adverse changes in venous valves and vein walls. The extent and rate of progression of the different changes will depend on the interplay of many factors, producing wide variation among patients.

Figure 3. Velocity of Blood Flow through a Venous Valve (Panel A) and Forces Acting on a Venous Valve Leaflet (Panel B).

In Panel A, the reduced cross-sectional area between the valve leaflets produces a proximally directed jet of increased axial velocity. In Panel B, axial flow between the leaflets generates a pressure (P_o) that tends to keep the leaflet in the open position, and vortical flow in the valve pocket generates a pressure (P_i) that tends to close the leaflet. These pressures depend on the respective flow velocities ($V_{vortical}$ and V_{axial}); pressure is inversely related to velocity. (Adapted from Lurie et al.[49] with the permission of the publisher.)

SKIN CHANGES

Venous hypertension seems central to the skin changes in chronic venous disease. In a sample of 360 lower limbs of patients with a wide spectrum of venous disease, there was a linear trend toward more severe skin damage with increasing postexercise venous pressure.[65] An increase in the occurrence of leg ulceration with increasing postexercise venous pressure was also observed in patients with chronic venous disease; the changes ranged from 0 percent venous ulceration in patients with postexercise venous pressures of less than 30 mm Hg up to 100 percent in patients with postexercise venous pressures of more than 90 mm Hg.[66] The proposal that cuffs of fibrin around dermal capillaries caused by filtration of fibrinogen could impede the diffusion of oxygen and lead to degenerative skin changes[67] has been superseded by the theory that chronic inflammation has a key role in skin changes of chronic venous disease.

Figure 4. Contrasting Effects of Steady, Laminar Shear Stress (Panel A) and Turbulent or Reversing Shear Stress (Panel B) on Vessel Walls.

NO denotes nitric oxide, MCP-1 monocyte chemoattractant protein 1, and VCAM-1 vascular-cell adhesion molecule. (Reproduced from Traub and Berk[50] with the permission of the publisher.)

CHRONIC INFLAMMATION

Current thinking about the basis of the skin changes in chronic venous disease can be traced back to the observation that the blood returning from feet that have been passively dependent for 40 to 60 minutes is depleted of leukocytes, especially in patients with chronic venous disease.[68,69] This finding suggests that leukocytes accumulate in the leg under conditions of high venous pressure. It is likely that the accumulation is largely due to leukocyte adhesion to, as well as migration through, the endothelium of small vessels, especially postcapillary venules. Another observation is that plasminogen activator is released into the congested vasculature, indicating that the accumulated leukocytes become activated. All this suggests that an inflammatory reaction is important in provoking skin changes in chronic venous disease.

Support for what has come to be known as the microvascular leukocyte-trapping hypothesis has come from immunocytochemical and ultrastructural studies that showed elevated numbers of macrophages, T lymphocytes, and mast cells in skin-biopsy specimens from lower limbs affected by chronic venous disease.[70,71] In rat models of both acute[72] and chronic[73] venous hypertension, elevated levels of tissue leukocytes were found in skin samples from affected legs, but not in those from sham-operated controls.

MECHANISMS OF INFLAMMATION

Circulating leukocytes and vascular endothelial cells express several types of membrane adhesion molecules. The transient binding of L-selectin on the leukocyte surface to E-selectin on endothelial cells underlies leukocyte rolling along the endothelial surface. When leukocytes are activated, they shed L-selectin into the plasma and express members of the integrin family, including CD11b, which binds to ICAM-1. Integrin binding promotes firm adhesion of leukocytes, the starting point for their migration out of the vasculature and degranulation.[74]

After venous hypertension was induced in patients with chronic venous disease by their standing for 30 minutes, levels of L-selectin and the integrin CD11b on circulating neutrophils and monocytes decreased, reflecting the trapping of these cells in the microcirculation. Simultaneously, plasma levels of soluble L-selectin increased, reflecting the shedding of these molecules from leukocyte surfaces during leukocyte–endothelial adhesion.[75] Basal plasma levels of the adhesion molecules ICAM-1, endothelial leukocyte-adhesion molecule 1, and vascular-cell adhesion molecule 1 were higher in patients with chronic venous disease than in control subjects, and increased significantly in response to venous hypertension provoked by standing.[76]

In addition to having local factors operating in relation to venous hypertension, patients with chronic venous disease tend to have a systemic increase in leukocyte adhesion. For example, plasma from patients with chronic venous disease induces more activation of normal, quiescent leukocytes (assessed by oxygen free radical production and pseudopod formation) than does plasma from control subjects.[77] The plasma factor responsible for this effect is unknown.
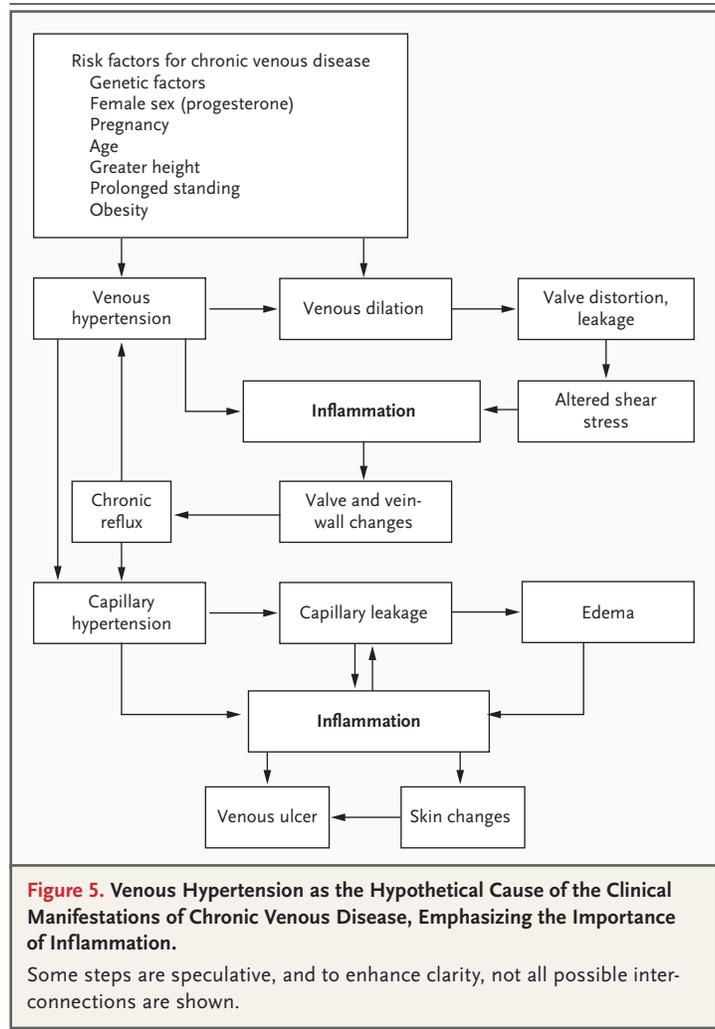
THE LINK BETWEEN INFLAMMATION AND SKIN CHANGES

The chronic inflammatory state in patients with chronic venous disease is related to the skin changes that are typical of the condition. Increased ex-

pression and activity of MMP (especially MMP-2) have been reported in lipodermatosclerosis,[78] in venous leg ulcers,[79] and in wound fluid from nonhealing venous ulcers.[80] In addition, levels of TIMP-2 are lower in lipodermatosclerotic skin and ulcers.[78,80] Unrestrained MMP activity may contribute to the breakdown of the extracellular matrix, which promotes the formation of ulcers and impairs healing.

In lipodermatosclerosis, the skin capillaries are elongated and tortuous,[81] and they may take on a glomerular appearance, with proliferation of the capillary endothelium in more advanced cases.[82] Vascular endothelial growth factor (VEGF), which is likely to be involved in these changes, has been shown to increase microvascular permeability.[83] Plasma levels of VEGF increased during the venous hypertension that was induced by 30 minutes of standing in control subjects and in patients with chronic venous disease, and the levels were higher in patients than in control subjects.[84] Furthermore, plasma VEGF levels were higher in patients with chronic venous disease with skin changes than in such patients with normal skin.[85]

Another feature of the skin changes associated with chronic venous disease is dermal tissue fibrosis. TGF-β_1 is a fibrogenic cytokine. In one study, skin from the lower calf of patients with chronic venous disease contained significantly elevated levels of active TGF-β_1 as compared with normal skin or skin from the thigh region of the same patients.[86] The TGF-β_1 was located in leukocytes and fibroblasts and on collagen fibrils. Pappas et al.[86] have proposed that activated leukocytes migrate out of the vasculature and release TGF-β_1, stimulating collagen production by dermal fibroblasts, which culminates in dermal fibrosis. Altered collagen synthesis by dermal fibroblasts in apparently healthy areas of skin in patients with varicose veins has also been reported.[87]

The hyperpigmentation of skin in lipodermatosclerosis may not be just an innocent by-product of capillary hyperpermeability. The extravasation of red cells leads to elevated levels of ferritin and ferric iron in affected skin.[88,89] These increases may cause oxidative stress, MMP activation, and the development of a microenvironment that exacerbates tissue damage and delays healing.[90] Consistent with this view, the hemochromatosis C282Y mutation (a common genetic defect of iron metabolism) is associated with an increase in

Figure 5. Venous Hypertension as the Hypothetical Cause of the Clinical Manifestations of Chronic Venous Disease, Emphasizing the Importance of Inflammation.

Some steps are speculative, and to enhance clarity, not all possible interconnections are shown.

the risk of ulceration by a factor of nearly seven in patients with chronic venous disease.[91]

IMPLICATIONS FOR TREATMENT

Although the causal and temporal sequences of events that occur during the development and progression of chronic venous disease have not been ascertained, the emerging twin themes of disturbed venous-flow patterns and chronic inflammation may underlie all the clinical manifestations of the disease (Fig. 5). Early treatment aimed at preventing venous hypertension, reflux, and inflammation could alleviate symptoms of chronic venous disease and reduce the risk of ulcers, both of which reduce the quality of life and are expensive to treat. Compression stockings improve venous hemodynamics,[92] reduce edema and skin discoloration,[93] and improve the quality of

life[94] in patients with chronic venous disease. Evidence is accumulating that surgery aimed at preventing venous reflux can aid healing and prevent the recurrence of ulcers[95,96]; it therefore seems reasonable to speculate that such treatment could reduce the risk of ulcers if performed early in the course of chronic venous disease. Treatment to inhibit inflammation may offer the greatest opportunity to prevent disease-related complications. Currently available drugs can attenuate various elements of the inflammatory cascade,[97,98] particularly the leukocyte–endothelium interactions that are important in many aspects of the disease.[46,99,100] These agents deserve detailed study. Overall, a determined and proactive approach to the treatment of the early stages of chronic venous disease could reduce the number of patients needing treatment for intractable ulcers. In the long term, improved understanding of the cellular and molecular mechanisms involved may allow the identification of additional targets for pharmacologic intervention.

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