Narrative Review of the Pathogenesis of Stasis Dermatitis: An Inflammatory Skin Manifestation of Venous Hypertension

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ABSTRACT

Introduction: Stasis dermatitis (SD), also known as venous dermatitis, is a form of inflammatory dermatitis of the lower extremities that typically occurs in older individuals and represents a cutaneous manifestation of venous hypertension. Venous hypertension (also known as sustained ambulatory venous pressure) is most often due to retrograde blood flow, which occurs due to calf muscle pump failure. This failure is most commonly secondary to incompetent venous valves, valve destruction, or obstruction of the venous system. Many of the common symptoms associated with SD are caused by inflammatory processes.

Methods: This review summarizes the pathogenesis and key role of inflammation in SD by reviewing inflammatory biomarkers associated with SD. The literature was selected though a high-level PubMed search focusing on keywords relating to inflammation associated with SD.

Results: Venous reflux at the lower extremities causes venous hypertension, which leads to

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chronic venous insufficiency. High venous pressure due to venous hypertension promotes the local accumulation and extravasation of inflammatory cells across the vascular endothelium. Leukocyte trapping in the microcirculation and perivascular space is associated with trophic skin changes. Cell adhesion molecules are linked with the perpetuated influx of activated leukocytes into inflammatory sites. Here, inflammatory cells may influence the remodeling of the extracellular matrix by inducing the secretion of proteinases such as matrix metalloproteinases (MMPs). The increased expression of MMPs is associated with the formation of venous leg ulcers and lesions. Phosphodiesterase 4 activity has also been shown to be elevated in individuals with inflammatory dermatoses compared to healthy individuals.

Discussion: Because inflammation is a key driver of the signs and symptoms of SD, several of the highlighted biomarkers of inflammation represent potential opportunities to target and interrupt molecular pathways of cutaneous inflammation and, therefore, remediate the signs and symptoms of SD.

Conclusion: Understanding the pathogenesis of SD may help clinicians identify drivers of inflammation to use as potential targets for the development of new treatment options.

pressure in leg veins. Several molecules are associated with the inflammation observed in stasis dermatitis, including white blood cells, matrix metalloproteinases, phosphodiesterase 4, and interleukin-31. Treatment for stasis dermatitis should focus both on the underlying chronic venous insufficiency and the associated skin issues. Identifying inflammatory markers and pathways could help treat the signs and symptoms associated with stasis dermatitis, including the skin symptoms.

Key Summary Points
Stasis dermatitis is caused by venous hypertension due to venous reflux.
If undiagnosed or left untreated, stasis dermatitis may be a precursor to venous ulcers.
Chronic inflammation represents the most likely link between the venous hypertension and cutaneous changes observed in stasis dermatitis.
Interrupting the molecular pathways that sustain cutaneous inflammation may remediate the signs and symptoms of stasis dermatitis.

PLAIN LANGUAGE SUMMARY

Stasis dermatitis is a skin disease that affects the legs, most often of older people, with chronic venous insufficiency. Chronic venous insufficiency is when veins cannot return blood from the legs back to the heart. This leads to high blood pressure in veins and causes blood in those veins to flow backwards. If stasis dermatitis is left untreated, complications, including skin ulcers, can result. Other skin symptoms of stasis dermatitis include itchiness, scaling, and discoloration. Such skin symptoms can have a negative effect on a person's quality of life. Inflammation that lasts a long time is likely the main link between the skin changes seen in people with stasis dermatitis and the increased

INTRODUCTION

Venous reflux at the lower extremities causes venous hypertension (also known as sustained ambulatory venous pressure), which leads to chronic venous insufficiency. Stasis dermatitis (SD), also known as venous dermatitis, is an inflammatory dermatitis of the lower extremities that predominantly affects older individuals with underlying chronic venous insufficiency [1, 2]. SD typically presents as bilateral

erythematous and eczematous patches and plaques of the lower extremities [3]. Estimates of the prevalence of chronic venous insufficiency vary widely depending on the characteristics of the populations examined. Approximately 2–6 million individuals in the USA have advanced forms of chronic venous insufficiency [2, 4]. In one study, SD was observed in 1.4% of individuals with varicose veins aged 15 years or more [5]. SD is more prevalent in older individuals and was found in 6.2% of individuals aged 65 years or more [6]. Results from similar studies indicated that SD was found in 5.9% of individuals with a mean age of 74 years (range 50–91 years) and in 6.9% of those with a mean age of 80 years (range 55–106 years) [2].

Early symptoms and signs of SD include pruritic, scaly, irritated, and discolored skin, especially in areas of the lower leg where varicose veins are present; additional symptoms and signs include aching and heaviness in one or both legs as well as swelling of the ankle and the lower leg [7]. The histologic epidermal changes linked to SD include hyperkeratosis, parakeratosis, acanthosis, and spongiosis. The histologic dermal changes associated with SD include extravasated erythrocytes, dermal fibrosis, perivascular lymphocytic infiltration, hemosiderin-laden macrophages, and proliferation of dilated small blood vessels with relatively thick walls in the papillary dermis [2]. SD is typically diagnosed on the basis of clinical findings and medical history [1, 8].

Several cutaneous disorders present similarly to SD, leading to misdiagnosis and mismanagement. More than 10% of cellulitis diagnoses are incorrect, with SD being the disease most frequently mistaken for cellulitis. Allergic forms of contact dermatitis are also often mistaken for SD. Moreover, allergic contact dermatitis may present simultaneously with SD, especially in patients with venous ulcers [1, 9]. SD can also resemble pigmented purpuric dermatoses, lymphedema, and sometimes neoplasms [1–3].

Several risk factors are associated with SD, including female sex, pregnancy, older age, obesity, prolonged immobility, family history of venous disease, chronic edema, heart failure, previous lower extremity trauma/surgery,

injection drug use, calf muscle injury, and a history of deep venous thrombosis [1, 8, 10, 11]. SD is more common in patients who are obese and/or pregnant, especially those who are multigravida, because of the extra stress that is placed on the veins of their lower extremities [12]. Immobile patients may also develop SD due to the reduced tone and contractility of the musculature at their lower extremities rather than anatomical complications of the venous system. Failure to activate the calf muscle pump because of angle joint issues or muscle disease can also lead to SD, even in the absence of venous changes [10, 11, 13].

SD is an indication of underlying vascular pathology and, if undiagnosed or left untreated, is a precursor to venous ulcers [1, 2]. As was found in one study, 37–44% of patients with leg ulcers were diagnosed with SD [14]. Approximately 2.2 million individuals in Europe and more than 6 million individuals in the USA experience venous leg ulcers [15]. Venous ulcers can occur as either a single or multiple ulcers and are often located over the medial malleolus (Fig. 1). Untreated SD can present with oozing and red, eroded, and/or scaly patches and plaques. Other skin changes may coexist. Contact dermatitis and autoeczematization due to SD can also arise [1]. Patients may also develop acroangiodermatitis [2, 16]. Additional presentations of the legs in patients with SD include swelling, itching, tingling, leg aching, restless legs, cramps, and lipodermatosclerosis [2]. Lipodermatosclerosis is an indurated plaque in the medial malleolus that can be exquisitely painful in its acute form, with the chronic form presenting with skin induration and hyperpigmentation of the legs [17–19]. Secondary infections may also occur because of the disruption of the epidermal barrier. Allergic contact dermatitis in SD may be caused by allergen penetration through the deteriorated epidermal barrier as well as contact with potential allergens that are applied during treatment. Autoeczematization, also referred to as an "id reaction," is the onset of a widespread, highly pruritic, erythematous, morbilliform or papulovesicular eruption in response to stimuli. The eruption often occurs at a distant location from the stimulus. Such stimuli could be due to

Fig. 1 Venous ulcers located over the medial malleolus. Note the presence of hyperpigmentation. Reprinted with permission from Ref. [68], with permission from Isabel C. Valencia et al., 2001, Chronic venous insufficiency and venous leg ulceration

a chronic inflammation from SD, contact dermatitis, or infections [1].

An improved understanding of the pathogenesis of SD could help in the development and utilization of more targeted and efficacious treatments. Accordingly, this review summarizes the pathogenesis and role of inflammation in SD. The PubMed literature search focused on keywords related to the inflammation associated with SD, including stasis dermatitis, varicose ulcers, venous stasis ulcers, stasis ulcers, venous ulcers, venous hypertension, varicose veins, venous eczema, venous stasis dermatitis, collagenases, dermatitis, inflammation, matrix metalloproteinases, and venous insufficiency. When indicated, venous intervention may remediate the underlying venous reflux associated with SD. When interventions are not feasible or fail, multiple long-term pharmaceutical and medical device options are available to treat the various dermatological symptoms associated with SD [1]. Non-invasive therapeutic approaches include leg elevation and walking [1]; however, such treatments were only shown to improve mild cases [2]. The initial treatment recommendation for SD is compression therapy in the form of compression bandages or stockings, which exert pressure to reduce ambulatory venous pressures, alleviating SD symptoms such as swelling and stasis skin changes

[1, 2, 13, 20–22]. However, compression therapy often fails because of the gradual loss of elasticity of the device or as a result of patient nonadherence with a treatment plan [1, 23]. It has been reported that only 50–60% of patients with SD adhere to compression therapy [24]. Skincare treatments such as bland emollients are often used to alleviate the secondary skin changes associated with SD, including scaliness and pruritus [2]. High- or mid-potency topical corticosteroids can be intermittently used to reduce pruritus and inflammation in SD. The prolonged use of corticosteroids should be avoided because they may lead to cutaneous atrophy and systemic side effects, potentially increasing the risk of ulcer formation [1, 25–28]. Topical calcineurin inhibitors can also be used for the management of SD; however, their use has been associated with burning upon application and requires patient awareness of potential and theoretical long-term complications (e.g., increased risk of elevated serum creatinine, hyperlipidemia, malignancy, and diabetes mellitus) [25–27, 29–32]. Venous interventions are also available to treat the underlying venous reflux. Interventional radiology and surgical interventions may lead to the resolution of SD. However, the recurrence of SD-related complications remains a problem regardless of the treatment used [1, 33]. There is therefore a need for novel therapies that can elicit anti-inflammatory effects and target the cutaneous manifestations of SD with optimized risk–benefit profiles. However, research regarding novel treatment options for SD is lacking [2]. Nevertheless, because inflammation plays a vital role in SD pathogenesis, several novel therapies that target inflammatory pathways could be promising. Such therapies include Janus kinase (JAK) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, and immunosuppressive therapies. A number of immunosuppressive therapies with anti-inflammatory properties, including azathioprine, cyclosporin, and mycophenolate mofetil, could also be potentially utilized in the treatment of SD [34–36]. Topical PDE4 inhibitors, such as crisaborole, could target the inflammation observed in SD while reducing unwanted side effects that are associated with systemic

treatments [25]. Studies regarding the evaluation of JAK inhibitors targeting receptor-associated kinases, such as delgocitinib, are also anticipated for SD [34].

This article is based on previously conducted studies and scientific literature and does not contain any new studies with human participants or animals performed by any of the authors. No ethics approval was necessary for this review.

Prompt treatment and diagnosis of SD could ameliorate potential future complications, such as ulcers [2]. General practitioners may not recognize the severity of venous disorders such as SD and thereby may not refer their patients to the appropriate specialists. Overall, the misdiagnosis of SD is partially due to the lack of dermatology services in healthcare settings [37, 38]. However, dermatologic consultation is often not considered by inpatient providers when treating patients with lower extremity inflammation. The introduction of educational campaigns regarding SD for general practitioners could promote the development of "champions of care" in healthcare settings who are able to promptly initiate the appropriate diagnosis and treatment of the disease. One study found that the average patient with SD was seen by about 6.9 doctors throughout the course of their treatment. However, the high number of consulted physicians in SD was mainly due to the patients' lack of adherence to treatment [38]. Accordingly, highlighting the importance of treatment adherence to patients could also improve disease outcome in SD.

PATHOGENESIS OF STASIS DERMATITIS

Venous Hypertension

SD is a cutaneous manifestation of venous hypertension that is the result of underlying chronic venous insufficiency [1, 2]. Chronic venous insufficiency of the lower extremities ranges from asymptomatic to severely symptomatic [39]. Chronic venous insufficiency has been clinically linked to sustained ambulatory venous pressures, whereby retrograde venous

blood flow is induced by incompetent venous valves and venous flow obstruction as part of calf muscle pump failure at the lower extremities [2, 40]. Such venous reflux can occur at the superficial venous system, the deep venous system, or both [40]. When valve failure occurs at the superficial and perforating veins, venous pressure in the veins and venules of the skin and subcutaneous tissues remains high during ambulation, whereas it typically diminishes in normal legs. Increased venous pressure may lead to the reversal of blood flow. Sustained elevated venous pressure leads to the margination and extravasation of cells from the blood vessels and into the surrounding tissues. Such blood flow patterns lead to the restructuring of the superficial veins and venules, which are less supported from a mechanical perspective than deep veins. Associated alterations include valve cusp perforation, elongation, tearing, and disappearance [41]. In one study that included patients with venous disease, primary valvular incompetence was found in approximately 70–80% of cases; such valvular incompetence was due to trauma or deep vein thrombosis in 18–25% of cases [40].

Venous hypertension is associated with elevated and unstable venous pressure values; such venous pressure is mainly driven by two components: a hydrostatic and a hydrodynamic component. The hydrostatic component is determined by the weight of the blood in the venous system, whereas the hydrodynamic component is determined by the pressure generated by leg skeletal muscle contractions and the pressure in the capillary network. While a person is standing, the hydrostatic component and the capillary flow determine the venous pressure in the legs, reaching values of 80–90 mmHg. During ambulation, skeletal muscle contractions increase the pressure observed in the deep leg veins, causing venous blood to return to the heart under normal physiologic conditions. Accordingly, competent venous valves ensure the blood's flow towards the heart, reducing venous pressure in the legs by emptying the superficial and deep venous systems and, hence, lowering the local venous pressure to less than 30 mmHg [2, 40, 41]. In the absence of competent valves, the reduction in

the venous pressure at the lower extremities that is brought upon by leg movement is attenuated. If the perforator venous valves of the deep venous system are incompetent, increased venous pressure is observed during standing as well as during calf muscle contractions, which leads to the reflux of blood into the superficial venous system and into the microcirculation in the skin. This results in an overall and continuous high-pressure system. Accordingly, the vessel walls of the superficial and deep venous systems are distorted, leading to a chronic cycle of worsening valvular incompetence and venous hypertension [1, 40]. Chronic elevation of venous pressure is linked to inflammatory reactions in the venous valves, eventually leading to venous reflux and dysfunction as well as the elevation of upstream venous pressure [41]. Impaired venous valves limit the return of blood to the heart, which leads to backward venous flow, venous hypertension, and venous stasis [2]. In one study that included 360 patients with SD, it was demonstrated that increases in ambulatory venous pressure are associated with severe skin damage, including ulceration [42]. In another study of patients that had negative patch testing and negative deep venous insufficiency, venous hypertension was found to be the most probable cause of SD, thus demonstrating that venous hypertension alone can cause SD in the lower extremities [2, 43]. In the same study, successful classical vein surgery that targeted superficial venous reflux, including saphenectomy of incompetent superficial vein segments and ligation of proximal point of reflux, led to the complete resolution of SD symptoms in treated patients. Here, the lower leg dermatitis healed rapidly, completely, and without recurrence for an observation period of 1 year [43].

Stasis Dermatitis is an Inflammatory Disease

Leukocytes and Cell Adhesion Molecules

The initial theory that the cutaneous changes in SD were driven by fibrin cuffs encasing dermal capillaries, thereby impeding the diffusion of oxygen from the vasculature and into epidermal cells, has been replaced by the understanding that inflammation plays a key role in the observed cutaneous changes. Indeed, chronic inflammation represents the most likely link between venous hypertension and cutaneous changes, as suggested by the correlation between such hypertension and inflammation [2, 40]. A major driver in the progression of uncontrolled inflammation in chronic venous insufficiency is the extravasation of leukocytes across the vascular endothelium. Such extravasated leukocytes infiltrate nearby tissues, secrete high levels of inflammatory mediators, and recruit inflammatory cells, thereby perpetuating the inflammatory response. Moreover, high venous pressure due to venous hypertension promotes the local accumulation of inflammatory cells, such as macrophages and T cells [2, 44]. Thomas et al. [45] found that leukocytes repeatedly accumulate in the microcirculation and perivascular space of extremities with venous hypertension. Such leukocyte trapping is commonly seen during the earlier stages of chronic venous insufficiency, particularly in cases of SD [43]. A parallel study that examined the lower extremities of patients with chronic venous insufficiency found that leukocytes and membrane adhesion molecules were more common on proximal venous valve surfaces and venous walls than on distal venous regions. Chronic venous reflux is associated with increases in leukocyte–endothelial cell interactions as well as an increase in the number of activated leukocytes. Unsteady stress alterations on the vein walls as well as venous distensions may lead to the activation of polymorphonuclear cells, macrophages, and endothelial cells [41]. Indeed, increased numbers of macrophages, mast cells, and T lymphocytes were observed in the skin biopsies of lower extremities in individuals with chronic venous insufficiency [46]. As a result, leukocytes become attached to the endothelium of the vein walls and valve leaflets, leading to the necrosis and/or apoptosis of the endothelium, fibroblasts, smooth muscle cells, and the parenchymal cells of the venous wall. These changes may promote weakening and destruction of the venous wall structures and valve leaflets, resulting in the clinically observable

venous changes [41]. The trophic skin changes seen in patients with venous hypertension may be due to the repeated accumulation of leukocytes in the microcirculation and the perivascular space [45]. Studies have shown that blood of the lower extremities in individuals with chronic venous disease is low in leukocytes, which suggests that leukocytes accumulate in regions of high venous pressure, leading to an inflammatory response [45–47]. Sustained high venous pressure also promotes the extravasation of erythrocytes at the affected regions [2, 44]. The extravasation of the erythrocytes is followed by the decomposition of hemoglobin, resulting in the excessive buildup of iron, which is stored at the affected tissue as hemosiderin and causes local hyperpigmentation. Further macrophage accumulation is induced by the buildup of the hemoglobin and hemosiderin; such macrophages alongside other cells promote inflammation (especially the accumulation of inflammatory macrophages) and induce the various histological features associated with SD, including vascular proliferation and epidermal spongiotic changes [44, 48]. The observed inflammatory response leads to local tissue damage [49].

The invasion of tissues by inflammatory cells is dependent on the transmigration of cells across the microvascular endothelium. This complex process of transmigration is mediated by cell adhesion molecules (CAMs). CAMs are expressed on the microvascular endothelial cells, whereas their receptors are found on the surface of leukocytes. The adhesion of leukocytes onto the endothelium is a multistep process [1, 2, 42]. The first step is the reversible binding of the endothelial cell selectin molecules, such as P-selectin and E-selectin, onto the sialyl Lewis X ligands on leukocytes. Leukocytes then firmly adhere onto the endothelial cells, which is required for the transmigration of leukocytes onto nearby tissues. This adhesion is mediated by intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), found on endothelial cells, and their ligands lymphocyte function-associated antigen 1 (LFA-1) and very late antigen 4 (VLA-4), which are found on leukocytes. ICAM-1, VCAM-1, LFA-1, and VLA-4 are upregulated

during the early stages of chronic venous insufficiency, including SD, and remain upregulated throughout latter stages (Fig. 2) [42, 43]. The highly expressed CAMs potentially promote skin tissue damage via the facilitation of an upregulated and perpetuated influx of activated leukocytes into the inflammatory sites [49]. Indeed, the aforementioned CAMs were found to be highly expressed on tissue-invading leukocytes and vascular endothelium at the edges of leg ulcers [50]. Such inflammatory changes lead to the release of several mediators, such as proteolytic enzymes, including collagenase and elastase, chemotactic factors, free radicals, and cytokines, which leads to an increase in vascular permeability [51].

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are associated with vascular disease and cardiovascular remodeling, as well as the turnover of elastin, collagen, and other proteins of the extracellular matrix. The results of studies regarding ulcer fluid environments suggest a potential association between the activity of MMPs and the development of venous leg ulcers and skin lesions. Imbalances between the expression and activity of MMPs and endogenous tissue inhibitors of MMPs (TIMPs) may cause pathological alterations of the vein walls and valves, leading to the symptoms associated with chronic venous diseases. Increases in venous hydrostatic pressure may lead to endothelial cell injury and increased cellular permeability, resulting in the infiltration of leukocytes and vascular inflammation into the surrounding dermis. This then leads to loss of wall integrity, tissue fibrosis, valve degradation, and vein damage that is characteristic of the late stages of chronic venous insufficiency [52].

Activated endothelial and inflammatory cells can degrade components of the extracellular matrix, including collagen, elastin, laminin, and fibronectin, through the release of oxygen free radicals and MMPs [42, 53]. Several MMPs were linked to the degradation of structure-maintaining collagen macromolecules, with MMP-1, -2, and -13 degrading type I, IV, and V collagens as well as elastin. These MMPs are
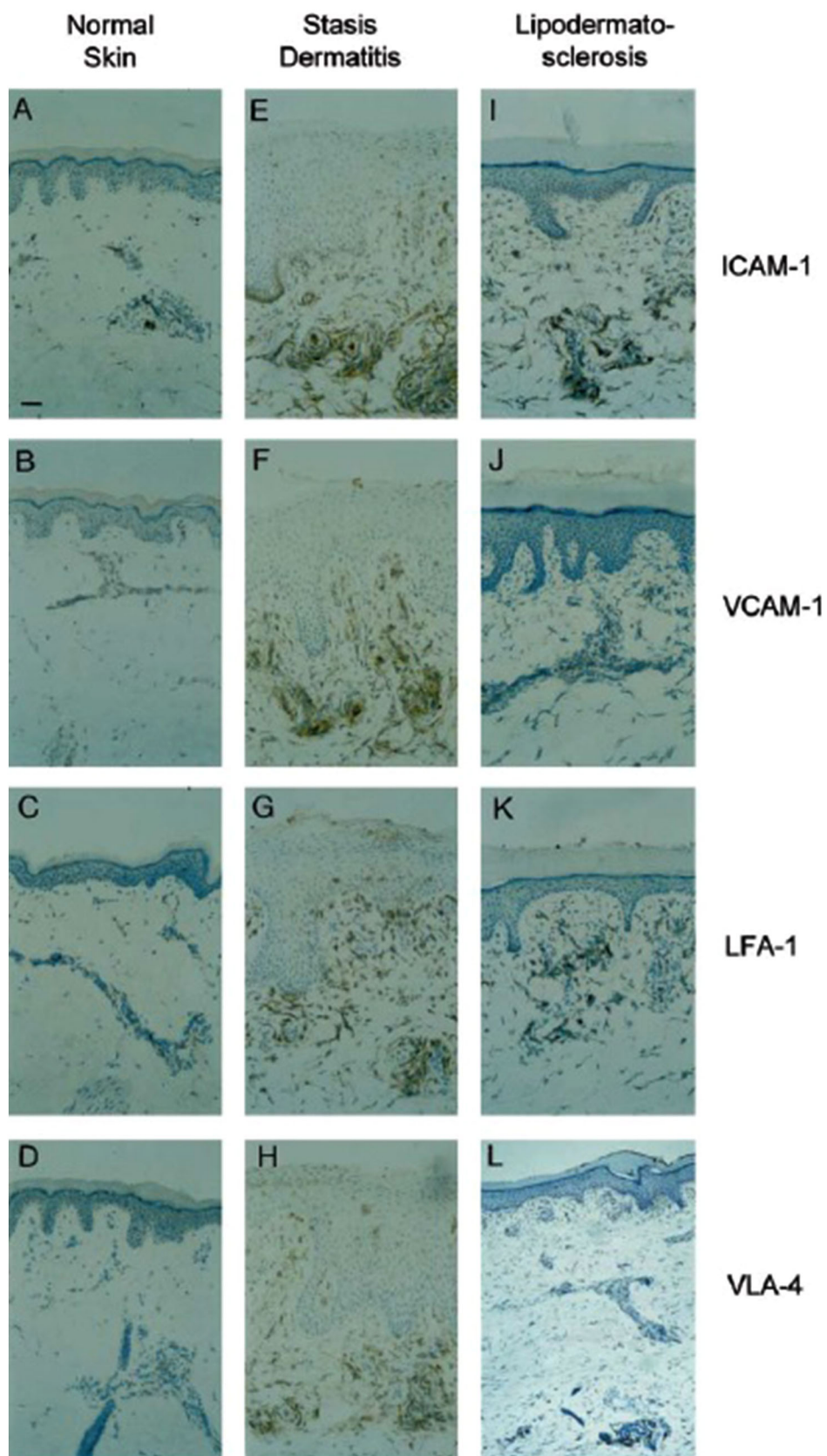
◁ **Fig. 2** ICAM-1, VCAM-1, LFA-1, and VLA-4 are
upregulated in stasis dermatitis and remain upregulated
in lipodermatosclerosis. Samples were obtained from
healthy individuals (**A–D**), patients with stasis dermatitis
(**E–H**), and patients with lipodermatosclerosis (**I–L**).
Cryosections of all skin samples were immunohistochem-
ically stained with monoclonal antibodies against ICAM-1,
VCAM-1, LFA-1, and VLA-4. The bar indicates a length
of 150 μm. Reprinted with permission from Ref. [34],
with permission from *Acta Dermato-Venereologica*. *ICAM-
1* intercellular adhesion molecule 1, *VCAM-1* vascular cell
adhesion molecule 1, *LFA-1* lymphocyte function-associ-
ated antigen 1, *VLA-4* very late antigen 4

secreted by inflammatory cells such as neu-
trophils, eosinophils, and macrophages. MMP-
1, -2, and -13 are associated with the patho-
genesis of several skin disorders, including basal
cell carcinoma, immune-bullous diseases, and
granuloma annulare [2, 54]. Inflammatory cells
influence the remodeling of the extracellular
matrix by producing MMPs and by secreting
cytokines that induce MMP gene expression,
including tumor necrosis factor-α, interleukin
(IL)-1, and transforming growth factor-$β_1$
(TGF$β_1$) [54]. The increased expression of MMPs
and other proteinases by the vessel wall breaks
down the vascular extracellular matrix, leading
to vascular permeability and edema [1]. Extra-
vasated erythrocytes release ferritin and ferric
ion, which may result in oxidative stress and
the activation of additional MMPs; this process
delays healing via promoting skin tissue dam-
age and ulcer formation [2, 40, 55]. Hyperpig-
mentation of the skin, which is observed in SD,
is due to hemosiderin deposition from extra-
vasated erythrocytes, activation of MMPs, and
inflammatory mediators [1, 2]. The activity of
MMPs is tightly regulated by their inhibitors,
TIMPs, with alterations in the balance between
MMPs and TIMPs contributing to the patho-
logical changes observed in venous diseases
[52]. In one study, elevated levels of MMP-1, -2,
and -13, as well as lower levels of TIMP-1 and -2,
were present in the skin samples of patients
with SD compared with healthy individuals.
Such overexpression of MMP-1, -2, and -13
without the inhibitory effects of TIMP-1 and -2
may be due to cytokine-mediated induction.

MMPs are associated with the degradation of
extracellular matrix proteins, potentially lead-
ing to the remodeling of lesional skin and
impaired healing in SD [54]. MMP-1, -2, and -13
may induce a number of histological features
observed in SD, including spongiosis, alteration
of papillary structures, and proliferation of
small blood vessels in the papillary dermis [2].
Alterations in MMP-2 activity, in conjunction
with events mediated via TGF$β_1$ (such as the
differentiation of fibroblasts into myofibrob-
lasts), were found to lead to the degradation of
epidermal basement membrane collagen and
the loss of epidermal integrity, creating an
environment that is susceptible to the forma-
tion of venous ulcers (Figs. 3, 4) [53].

Phosphodiesterase 4

PDE4 is a cyclic adenosine monophosphate
(cAMP)-specific intracellular nonreceptor
enzyme that regulates various fundamental
functions, including inflammatory responses, as
well as epithelial and endothelial barrier stabil-
ity [25, 56, 57]. Patients with inflammatory
diseases show elevated levels and activity of
PDE4 compared with healthy individuals. As
has been shown in studies, the overexpression
and overactivity of PDE4 leads to increases in
the production of inflammatory cytokines
(Fig. 5), causing skin inflammation and disease
exacerbation in patients with atopic dermatitis.
The inhibition of PDE4 elevates intracellular
cAMP levels, thereby modulating the inflam-
matory response and maintaining the immune
balance. Targeting PDE4 has been shown to be
an effective strategy for several inflammatory
conditions, including psoriasis, atopic dermati-
tis, chronic obstructive pulmonary disease,
asthma, inflammatory bowel diseases, rheuma-
toid arthritis, lupus, and neuroinflammation
[56]. Accordingly, the inhibition of PDE4 may
decrease the production of inflammatory
cytokines, thereby limiting associated skin
inflammation and disease exacerbation in SD
[58, 59]. Emerging therapies for the treatment
of secondary skin changes associated with SD
such as skin inflammation could involve the
application of nonsteroidal topical ointments,
such as crisaborole. Crisaborole is a topical
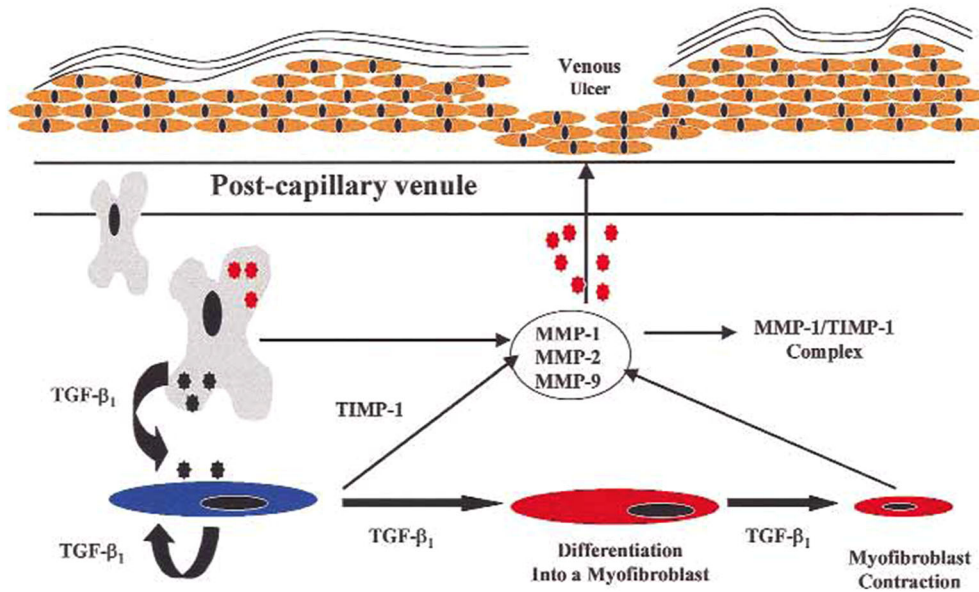PDE4 inhibitor that has been approved for the

Fig. 3 The possible roles of MMPs and TGFβ_1 in the formation of venous ulcers. Reproduced from Ref. [38], with permission from Elsevier. *MMP* matrix metalloproteinase, *TGFβ_1* transforming growth factor-β_1, *TIMP-1* tissue inhibitor of metalloproteinase-1
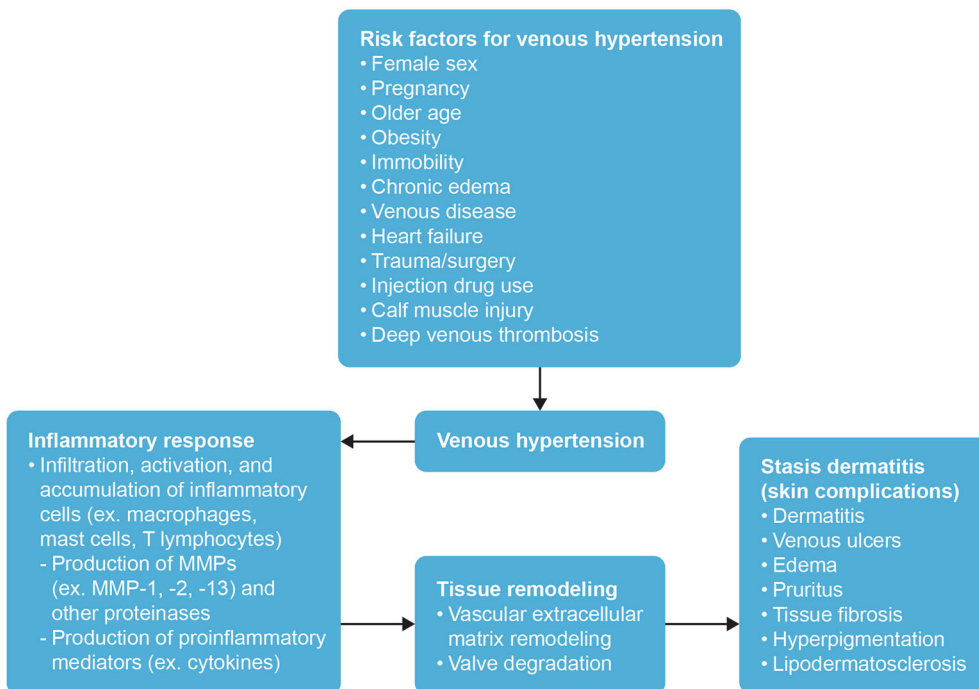
Risk Factors for Stasis Dermatitis

Risk factors for venous hypertension
- Female sex
- Pregnancy
- Older age
- Obesity
- Immobility
- Chronic edema
- Venous disease
- Heart failure
- Trauma/surgery
- Injection drug use
- Calf muscle injury
- Deep venous thrombosis

Venous hypertension

Inflammatory response
- Infiltration, activation, and accumulation of inflammatory cells (ex. macrophages, mast cells, T lymphocytes)
  - Production of MMPs (ex. MMP-1, -2, -13) and other proteinases
  - Production of proinflammatory mediators (ex. cytokines)

Tissue remodeling
- Vascular extracellular matrix remodeling
- Valve degradation

Stasis dermatitis (skin complications)
- Dermatitis
- Venous ulcers
- Edema
- Pruritus
- Tissue fibrosis
- Hyperpigmentation
- Lipodermatosclerosis

Fig. 4 Pathophysiology of stasis dermatitis. *MMP* matrix metalloproteinase
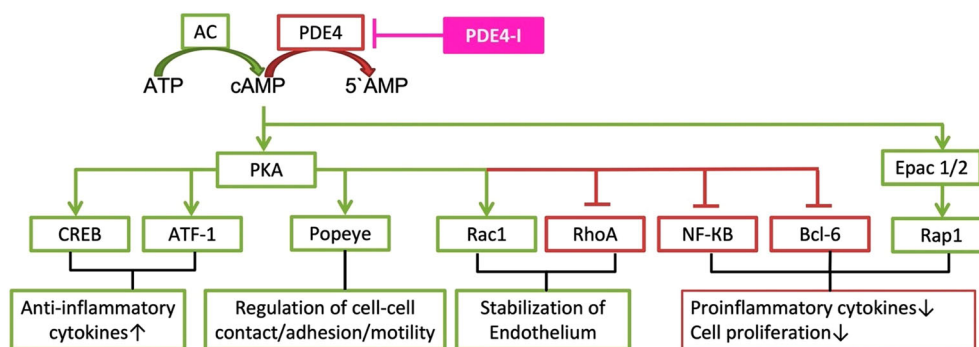
Fig. 5 The cAMP cascades involved in PDE4 inhibition. Reproduced from Ref. [48], with permission from MDPI (Basel, Switzerland). *5′AMP* 5-adenosine monophosphate, *AC* adenylyl cyclase, *ATF-1* cAMP-dependent activating transcription factor 1, *ATP* adenosine triphosphate, *Bcl-6* B cell lymphoma 6 protein, *cAMP* 3′,5′-cyclic adenosine monophosphate, *CREB* cAMP response element binding protein, *Epac 1/2* exchange protein directly activated by cAMP 1 and 2, *NF-κB* nuclear factor kappa light chain enhancer of activated B cells, *PDE4* phosphodiesterase 4, *PDE4-I* phosphodiesterase 4 inhibitor, *PKA* protein kinase A, *Popeye* Popeye domain family, *Rac1* Ras-related C3 botulinum toxin substrate 1, *Rap 1* Ras-related protein 1, *RhoA* Ras homolog family member A

treatment of mild-to-moderate AD in multiple countries and was recently investigated in a phase 2 study for SD treatment (NCT04091087) [60, 61].

Interleukin-31

Patients with SD often report having pruritus, which impairs quality of life and induces further cutaneous irritation and breakdown due to excessive scratching [1, 44]. Indeed, SD was the most frequently reported type of dermatitis to cause itch complaints in one study involving older adults [62]. Constant scratching aggravates wounds and increases the chances of developing skin infections; it may also result in skin thickening and lichenification [1, 44]. The pathogenesis of SD-linked pruritus is incompletely understood; however, it is likely nonhistaminergic because it is not remediated by use of antihistamines. Nonhistaminergic itch involves several itch mediators, such as cytokines/chemokines (e.g., IL-31), proteases and their receptors, amines, neuropeptides and their receptors (e.g., substance P and its receptor neurokinin-1 receptor), ion channels, and immune cells (e.g., mast cells, T cells, eosinophils, and basophils) [44]. IL-31 is a T-helper type (Th)2-related pruritogenic cytokine that has recently been implicated as a potential target for skin conditions involving itch. IL-31 is associated with exacerbating pruritus in various diseases, including psoriasis, atopic dermatitis, prurigo nodularis, and cutaneous T-cell lymphoma [63–65]. Increased IL-31 expression is found in the skin of patients with atopic dermatitis, prompting the release of inflammatory mediators and lowering the expression of molecules associated with maintaining the skin barrier [66]. The correlation between pruritus and IL-31 was highlighted in a study in which serum levels of IL-31 were found to be significantly higher in patients with chronic pruritus of unknown origin compared with those in healthy individuals [67].

A recent study has implicated dermal IL-31 from macrophages in inducing itch in SD [44]. The majority of IL-31-expressing cells in SD are $CD68^+$ macrophages. The number of $IL-31^+CD68^+$ macrophages is significantly higher in patients with SD with severe pruritus compared with those with SD without severe pruritus. These $CD68^+$ macrophages, which also coexpress CD163 (a macrophage-specific membrane marker), are classified as M2 macrophages (Fig. 6) [66]. The number of $IL-31^+CD68^+$ macrophages is positively correlated with the number of dermal C–C chemokine receptor type 4^+ Th2 cells, basophils, and substance P^+ cells, as well as dermal deposition of hemosiderin and periostin. Moreover, the number of
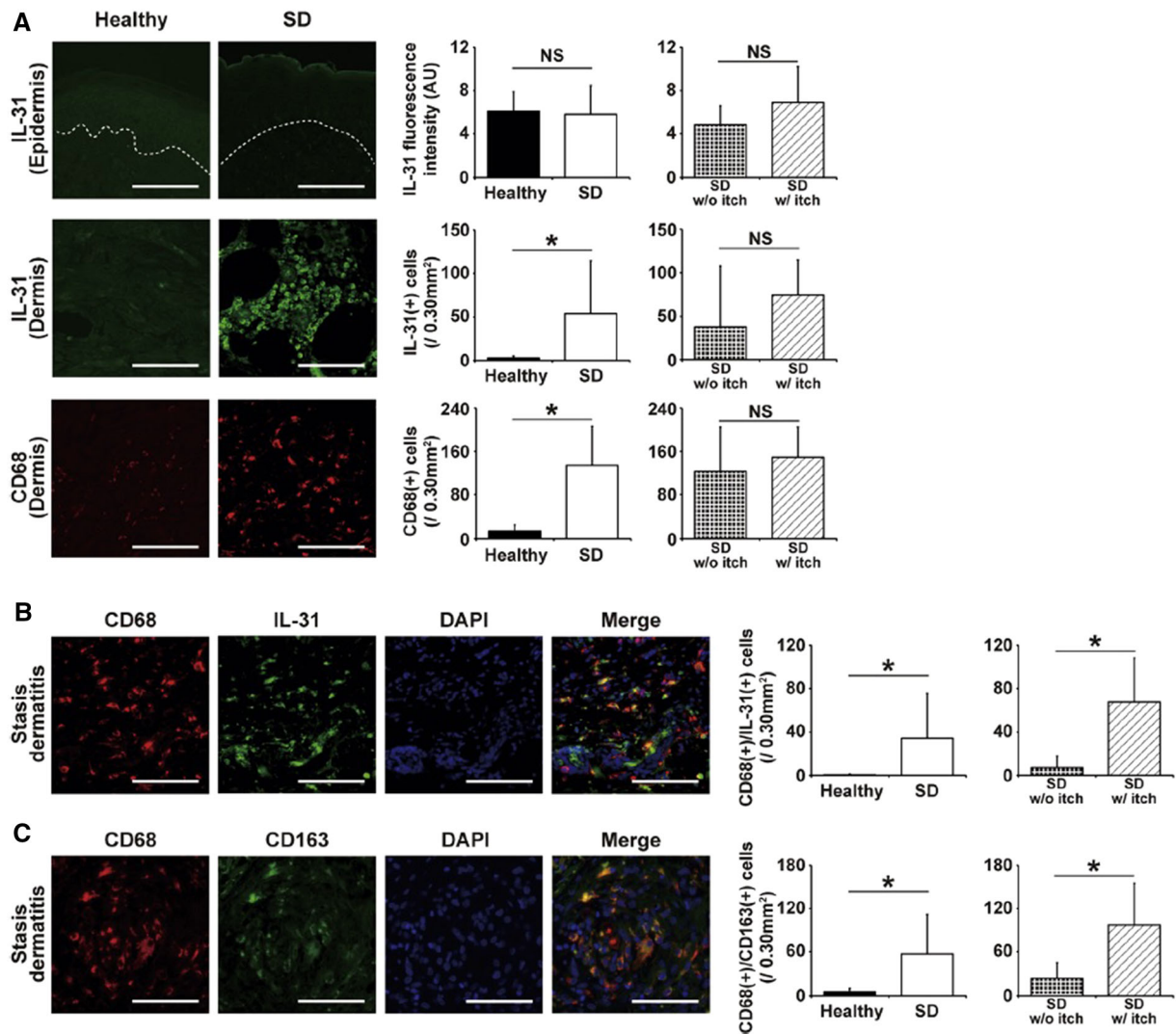
Fig. 6 CD68^{+} macrophages express IL-31 and are correlated with pruritus in SD. Images of healthy skin and SD lesions with the quantification of staining are shown. **a** Epidermal expression of IL-31 was not higher in SD lesions. The number of CD68^{+} macrophages and IL-31^{+} cells was greater in SD lesions. **b** Most IL31^{+} cells expressed CD68. The number of CD68^{+}/IL31^{+} cells was greater in SD lesions and was correlated with pruritus. **c** In SD with severe pruritus, CD68^{+} macrophages expressed CD163 (an M2 macrophage marker). The number of CD68^{+}/CD163^{+} cells was greater in SD lesions and correlated with pruritus. *$P < 0.05$ (unpaired *t* test). Vertical bars indicate standard deviation. Dotted lines indicate the dermo-epidermal junction. The bar indicates 100 μm. Reproduced from Ref. [29], with permission from Elsevier. *AU* arbitrary unit, *CD* cluster of differentiation, *DAPI* 4′,6-diamidino-2-phenylindole, *IL-31* interleukin-31, *NS* not significant, *SD* stasis dermatitis, *w/* with, *w/o* without

IL-17^{+} cells is also higher in SD lesions, which is consistent with Th17 immunity predominating in SD. The number of IL-17^{+} cells is correlated with the number of IL-31^{+}CD68^{+} cells but not with the presence of pruritus. IL-17 likely promotes M2 macrophage skewing, with M2 macrophages promoting Th17 cell expansion [44].

CONCLUSIONS

SD is a cutaneous manifestation of venous hypertension that is commonly seen in older patients with underlying venous insufficiency, wherein retrograde venous blood flow is induced by incompetent venous valves, venous flow obstruction, or muscle pump failure at the lower extremities. Treatments for SD focus primarily on identifying and eliminating primary causes of venous hypertension and insufficiency when feasible and, secondarily, on management of associated skin changes as well as preventing potential complications. Understanding the pathogenesis of SD may help clinicians effectively diagnose and treat SD. Several of the highlighted biomarkers of inflammation represent potential opportunities to individually or jointly interrupt molecular pathways which sustain cutaneous inflammation and, therefore, remediate the signs and symptoms of SD that diminish quality of life in patients with SD.

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