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REVIEW

Controversies in the pathophysiology of leg ulcers in sickle cell disease

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Summary

Patients with sickle cell disease (SCD) often experience painful vaso-occlusive crises and chronic haemolytic anaemia, as well as various acute and chronic complications, such as leg ulcers. Leg ulcers are characterized by their unpredictability, debilitating pain and prolonged healing process. The pathophysiology of SCD leg ulcers is not well defined. Known risk factors include male gender, poor social conditions, malnutrition and a lack of compression therapy when oedema occurs. Leg ulcers typically start with spontaneous pain, followed by induration, hyperpigmentation, blister formation and destruction of the epidermis. SCD is characterized by chronic haemolysis, increased oxidative stress and decreased nitric oxide bioavailability, which promote ischaemia and inflammation and consequently impair vascular function in the skin. This cutaneous vasculopathy, coupled with venostasis around the ankle, creates an ideal environment for local vaso-occlusive crises, which can result in the development of leg ulcers that resemble arterial ulcers. Following the development of the ulcer, healing is hindered as a result of factors commonly observed in venous ulceration, including venous insufficiency, oedema and impaired angiogenesis. All of these factors are modulated by genetic factors. However, our current understanding of these genetic factors remains limited and does not yet enable us to accurately predict ulceration susceptibility.

KEYWORDS
chronic wounds, leg ulcers, pathophysiology, sickle cell disease, treatment

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive genetic disorder secondary to a single mutation in the β-globin gene. Sickle cell anaemia (SCA; HbSS) is the most common and the most severe form of SCD.[1] Data from the United States, from 1989 to 2012, report that, for every 1941 newborn births screened, one case of SCD was identified and one of every 67 neonates screened was heterozygous for the beta-S allele.[2]

The primary mechanism at the origin of the complex SCD pathophysiology is HbS polymerization in deoxygenated conditions,[3] which causes the sickling of red blood cells (RBCs). Sickled RBCs are poorly deformable and very fragile, putting patients with SCD at risk for repeated painful vaso-occlusive crises and chronic haemolytic anaemia.[4] Patients with SCD are not only at risk of developing various acute complications but may also develop chronic complications, including leg ulcers. Chronic leg ulceration in SCD has been associated with significant clinical and psychosocial morbidity[5–7] and an increased risk of early death.[8] Prevalence of chronic leg ulcers among individuals with SCD varies from 1.4% in Brazil to 29.5% in Jamaica.[9–13]

In order to improve the management and care of SCD leg ulcers, the mechanisms behind their occurrence must be

better understood. In this review, we aim to explore several contentious aspects of the current understanding of leg ulcer pathophysiology in SCD and examine potential factors contributing to their delayed healing.

SCD ULCERS START MOSTLY LIKE AN ISCHAEMIC ULCER

Ulcerations in SCD are likely caused by local vaso-occlusive crises, resulting in cutaneous microvascular infarctions. The majority of SCD ulcerations manifest spontaneously, without any associated trauma.[5] Patients usually experience the initial symptom of spontaneous pain, followed by induration, hyperpigmentation or subcutaneous necrosis, blister formation and destruction of the epidermis.[5] In some patients, leg ulcers may occur after minor trauma or scratching.[5,14] However, irrespective of the mode of onset, the progression of the ulcer tends to follow a similar course.[5]

General conditions

Several studies reported a high incidence of leg ulcers in males compared to females with SCD.[11,13,15–18] The male to female ratio was approximately 2 in the United States and Nigeria.[16,17] In contrast, other studies reported a similar incidence between males and females.[9,12,15,19] Thus, no clear conclusion about the effect of gender on ulceration can be drawn from the literature.

In addition, it has been observed that patients with leg ulcers tend to have poorer social conditions.[10] Cumming et al. reported that, in a Jamaican cohort of individuals with SCD, 85% of patients with leg ulcers were below the poverty line, whereas only 46% of those without leg ulcers fell below the poverty line.[9] It remains challenging to determine whether the incidence of leg ulcers is related to housing or working conditions. As discussed below, oedema can delay healing,[20] and factors such as prolonged standing or sleeping in a seated position can exacerbate oedema.[21] SCD patients with leg ulcers should be questioned about their living conditions (Figure 1). Physicians should emphasize the importance of leg care to their patients and specify that if oedema occurs, they should elevate their legs whenever possible to prevent leg ulcers and minimize healing delays. Depending on the country in question, social workers may have varying capacities to assist SCD patients with housing conditions and financial support.

In SCD patients, poor social conditions may also contribute to malnutrition. Malnutrition, which can be characterized by a low serum albumin level[19] or a low body mass index (BMI),[11,19] has been linked to the occurrence of leg ulcers in SCD patients. In general, malnutrition, a common factor among patients suffering from wounds,[22] may precede the appearance of ulcers and promote wound development or appear during the healing process. The importance of nutritional management has been well established in other types of chronic wounds[23] and is likely fundamental in treating leg ulcers in SCD patients. It is important to note that nephropathy or liver disease may also contribute to a low

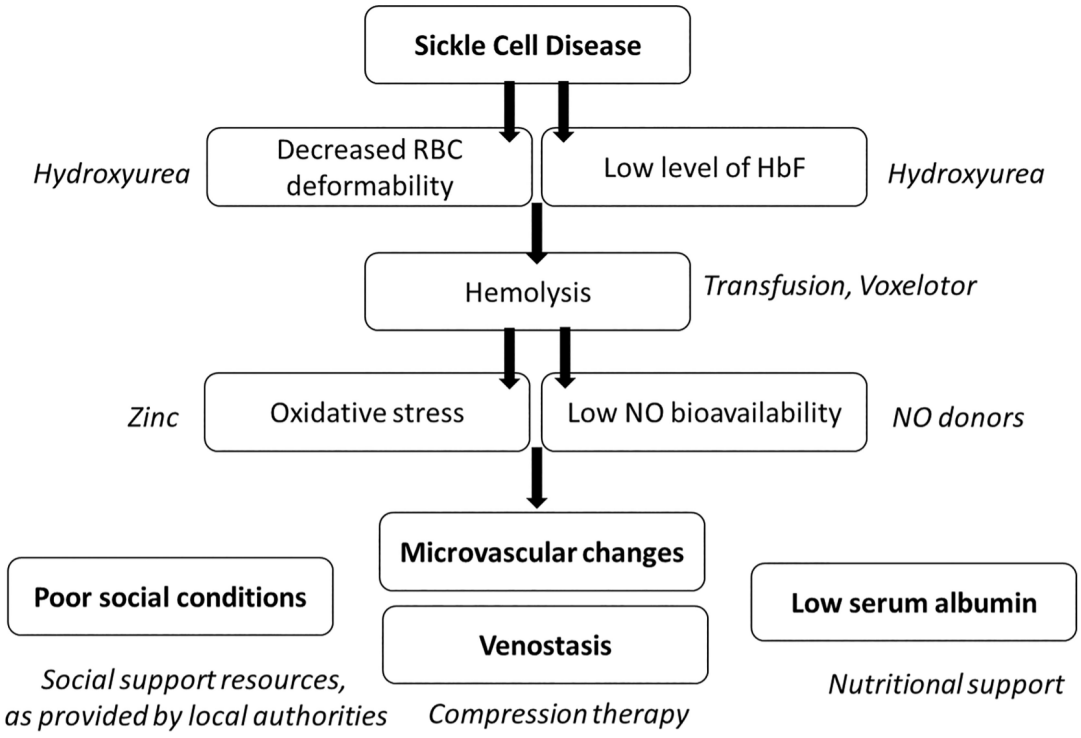

FIGURE 1 Treatments focusing on some of the mechanisms involved in leg ulcer occurrence in sickle cell disease patients.[14,40,44,98,110,119,120]

serum albumin level.[24,25] Therefore, laboratory tests should include measurements of albumin and pre-albumin to check for malnutrition, as well as creatinine, ALT (alanine amino transferase), ASAT (aspartate amino transferase), GGT (gamma glutamyl transferase) and alkaline phosphatase to screen for the presence of glomerulopathy and liver disease (Figure 1).

Vascular modifications

Microvascular changes can lead to inadequate tissue perfusion, an important factor in the development of chronic wounds and delayed healing. In SCD patients, microscopic examination of leg ulcer beds has revealed evidence of vasculopathy.[15] This includes activated capillary endothelium, signs of thrombosis/recanalization and neovascularization around occluded capillaries[15,26] and inflammation.[15] The progression of these microvasculopathies varies depending on the patient's age, although the first ulcers may appear as early as age 10.[5,9,12,27]

Additionally, capillary blood stasis and venostasis have been observed through microscopic examination[15] and laser Doppler.[28] Venostasis is favoured by the abolition of the venoarteriolar reflex and cardiovascular autonomic dysfunction.[29] The resulting pressure from venostasis is greatest in the peri-malleolar region, which is the primary site for SCD leg ulcers.[5,30] Stasis may also facilitate local sickling due to prolonged exposure of RBC to hypoxia and local vaso-occlusive crisis, increasing the risk of leg ulcer development.[31] There is no evidence to support the efficacy of compression therapy with socks on leg ulcers in the absence of oedema (Figure 1). When legs are in a hanging position, inappropriate vasoconstriction has been observed around SCD ulcers,[32] which could potentially contribute to delayed healing. Macrovascular abnormalities have also been observed in SCD patients with leg ulcers, suggesting involvement of diffuse vasculopathy, including increased intima media thickness in the femoral arteries.[33]

The following sections will focus on the proposed mechanisms underlying vasculopathy in both the macro- and microcirculation.

Haemolysis

Sickle RBCs are prone to lysis[34] and the extent of haemolysis has been associated with the occurrence of leg ulcers.[35] Common markers of haemolysis in SCD patients with leg ulcers are high levels of LDH, bilirubin, aspartate aminotransferase and reticulocytes, concomitant with low haemoglobin levels.[10,11,19,36,37] A recent study conducted in Senegal and Mali and that included 235 SCD adults found no difference in LDH and bilirubin levels between those with and without leg ulcers,[38] suggesting that haemolysis may not be the sole contributing factor to leg ulcer development, particularly in regions where clinical management and therapeutic options differ from those in developed countries. Nevertheless, Minniti et al. observed clinical improvement in leg ulcers among SCD patients participating in the phase III, randomized, double-blinded, placebo-controlled, HOPE trial (NCT03036813), which evaluated the effects of Voxelotor.[39] Voxelotor is a novel molecule that inhibits HbS polymerization by increasing the affinity of HbS to oxygen (Figure 1). Voxelotor has been shown to reduce haemolysis and increase haemoglobin levels.[40] A new randomized controlled trial (RCT) called RESOLVE is currently recruiting SCD patients to specifically study the effect of Voxelotor on leg ulcer healing (NCT05561140).

Haemolysis results in reduced nitric oxide (NO) bioavailability[41] and aberrant vascular activity, leading to tissue ischaemia and ulcer formation.[15,42] In SCD patients with leg ulcers, Landburg et al. observed the elevated levels of asymmetric dimethylarginine, an inhibitor of NO synthase released during haemolysis.[43] Minniti et al. observed increased peri-wound cutaneous blood flow measured by laser speckle contrast imaging and infrared thermography in 18 SCD patients with leg ulcers after applying a topical NO donor.[44] Moreover, leg ulcer size and pain decreased in a dose-dependent manner (Figure 1). Ulcers healed completely in three patients who received the highest concentrations of topical sodium nitrite cream (1.8% and 2%). A phase II study is ongoing in SCD patients with leg ulcers (NCT02863068).

Reduced NO bioavailability is also associated with increased inflammation.[45,46] Pathologists have observed an inflammatory infiltration of white blood cells in SCD ulcer tissues.[15,26,47] The plasma levels of several pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and IL-15) were found to be significantly elevated in the serum of SCD patients with leg ulcers compared to those without.[48–50] In an attempt to control the inflammatory process, the anti-inflammatory cytokine IL-10 level was shown to be increased in the plasma[51] and in cultures of peripheral blood mononuclear cells of SCD patients with leg ulcers compared to those without.[52]

In SCD, the most rigid RBCs are also the most fragile.[34] Therefore, a greater impairment in RBC deformability likely accounts for the increased haemolysis in patients with leg ulcers.[53–55] The reduced RBC deformability could decrease tissue oxygenation and participate in leg ulcer onset.[53–55]

Lastly, the percentage of fetal haemoglobin (HbF) determines the propensity of RBCs to sickle upon deoxygenation.[56] Thus, any factors/mechanisms that may stimulate the production of HbF may decrease haemolysis and modulate the clinical expression of SCD.[56] A number of studies have highlighted the association between low HbF levels and leg ulcer development.[9,27,37,57,58]

HU is the most common drug used to treat SCD patients. HU improves anaemia by increasing HbF expression, which decreases HbS and its polymerization under deoxygenated conditions, thus reducing haemolysis.[59] Indeed, HU reduces RBC sickling and fragility.[59] The clinical experience with HU in patients with leg ulcers is paradoxical. While it may be expected that HU would reduce leg ulcer incidence, the literature reports several cases of leg

ulcers in patients treated with HU.[60–63] Soya et al. reported a case of an SCD patient who developed a leg ulcer 18 days after the introduction of HU and healed after HU was stopped.[64] The authors proposed that the accumulation of HU under the skin could have caused cutaneous atrophy and impaired microcirculation.[64] An alternate hypothesis could be that the level of HbF reached during HU treatment was not enough to provide clinical benefits. Recently, Tolu et al. identified that an HbF level >25% would be necessary to limit leg ulcer development in SCD patients treated with HU,[65] a level rarely achieved. However, data from the ESCORT-HU study (a Phase IV observational cohort study including 1906 SCD patients treated with HU to the study safety profile) are reassuring. In this study, leg ulcers were reported in only 33 patients, corresponding to an incidence of 1.73%.[66] ESCORT-HU extension is currently recruiting to improve knowledge about HU and leg ulcers (NCT04707235).

Two biological/clinical phenotypes have been distinguished in SCD. One phenotype is characterized by the presence of high viscosity, which increases the risk for painful vaso-occlusive crisis, acute chest syndrome and osteonecrosis.[35,67] The other phenotype, called the haemolytic–endothelial dysfunction phenotype, is characterized by more severe haemolysis, which leads to the development of progressive vasculopathy, and an increased risk of leg ulcers, priapism, cerebral vasculopathy, glomerulopathy and pulmonary hypertension. Many studies have shown an association between leg ulcers and echocardiographic signs of pulmonary hypertension.[13,19,68,69] Parent et al. confirmed these results using right heart catheterization,[70] the gold standard for pulmonary hypertension diagnosis. These observations support systematic screening of pulmonary hypertension in SCD patients with leg ulcers. In addition, Nolan et al.[36,71] and others[10,15] have identified an association between leg ulcers and priapism.

Genetic studies

Haemoglobin genotypes, co-existing α-thalassaemia and β^S haplotypes

Powars et al. hypothesized that each SCD patient has a predetermined rate of disease progression,[72] with genetic factors dominating the biological calendar that controls vasculopathy development (Figure 2).[72] Four region-specific African haplotypes (Senegal, Benin, Bantu also called CAR β for Central African Republic and Cameroon haplotypes) and the Arab-India haplotype have been defined.[73] The CAR β haplotype has been associated with a higher incidence of soft tissue organ failure (including central nervous system, kidney, lung and leg ulcers).[72] However, Powars et al.[72] were the only authors to report this association, and the haplotype characterization is not systematic in SCD centres worldwide. In the Nolan study, the βS haplotypes were not associated with leg ulcers.[36]

Haemolytic rate also depends on haemoglobin genotype, with HbSS and HbSβ^0 patients exhibiting higher level of haemolysis. Indeed, it is not surprising to observe more leg ulcers in these patients than in HbSβ^+ and HbSC patients.[5,11,27,72] Moreover, since the coexistence of α-thalassaemia modulates the degree of haemolysis, some studies logically found that patients with 2 α-gene deletions have a lower risk of developing leg ulcers.[27,36,74] Other studies failed to find an association between leg ulcer incidence and α-thalassaemia.[9,19,55,75] Minniti et al. proposed that these apparently conflicting results could be due to the small number of subjects with α-thalassaemia in certain studies, resulting in low statistical power, which reduces the chances of detecting a true effect.[19] Thus, SCD patients without α-thalassaemia may be at an increased risk of developing leg ulcers and should be advised to consult their doctor immediately if they incur an ankle wound.

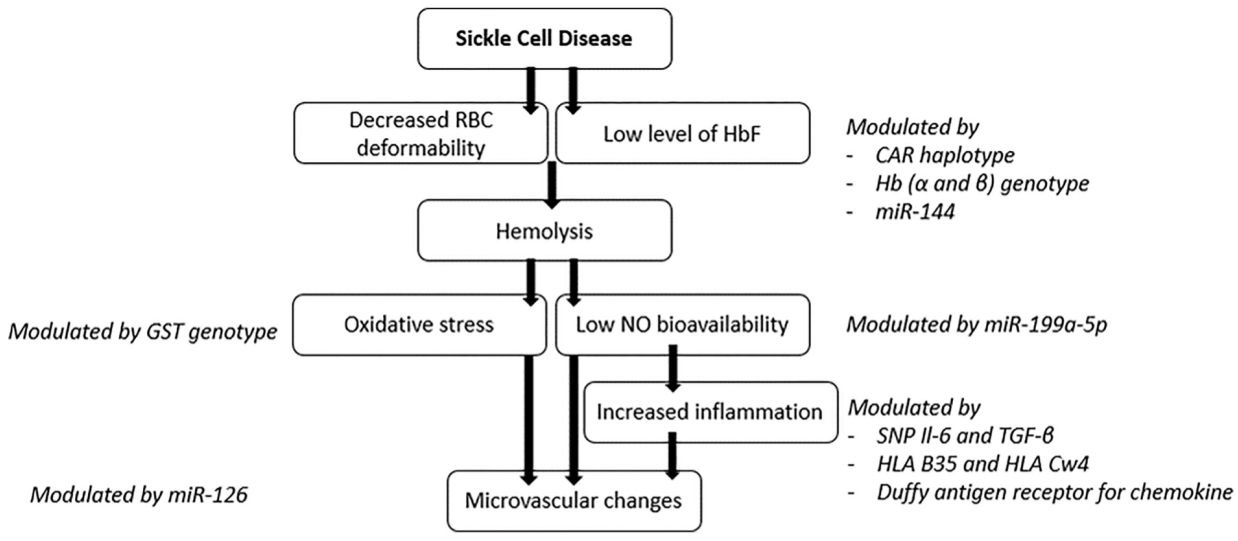

FIGURE 2 Reported genetic associations with some mechanisms involved in leg ulcer occurrence in SCD patients. GST, glutathione S transferase.

Immunity

Human leucocyte antigens (HLA) constitute a complex genetic system that encodes proteins which predominantly regulating immune/inflammatory processes. The relative risk of developing leg ulcers in SCD patients who had both HLA-B35 and HLA-Cw4 was found to be 17 times higher compared to patients without these HLAs.[76] These results suggest that genetic factors from the HLA system may contribute to the development of leg ulcers in SCD patients.[76] HLA-B35 has been linked to increased susceptibility to apoptosis[77] and endothelial dysfunction through higher production of endothelin-1 (ET-1).[78] However, the causal relationship remains elusive.

Humoral immunity may also play a role in leg ulcer risk. Namely, a single nucleotide polymorphism (SNP) of *IL6* has been proposed as a potential risk factor for leg ulcers.[50] The influence of the Duffy antigen receptor for chemokines (DARC) has also been studied in the context of SCD. DARC modulates the inflammatory process depending on its expression level. While some studies did not report any association between the occurrence of leg ulcers and DARC expression,[79,80] Drasar et al. found an increased incidence of leg ulcers when DARC expression was high.[81] It has been suggested that DARC could play a role in the recruitment of white blood cells that could participate to vascular occlusion and initiate leg ulcers.[81] These findings corroborate the high level of inflammation in and around the leg ulcers mentioned above. However, there is currently no treatment targeting inflammation.

miRNA

MicroRNAs (miRNAs) are small non-coding RNAs involved in post-transcriptional gene repression by influencing messenger RNA (mRNA).[82] The processing of primary miRNA transcripts into mature miRNAs is a regulated multistep process, and its deregulation is often associated with human diseases.[83]

Increased expression of circulating miR-199a-5p and miR-144 has been reported in SCD patients with leg ulcers, while miR-126 expression was reduced.[84,85] MiR-199a-5p has been shown to regulate NO production by endothelial NO-synthase in vitro[86] and may also have a regulatory role in cardiomyocytes,[87] cancer cell proliferation[88] and bile acid efflux transport.[89] MiR-144 may regulate various processes such as HbF production through gene silencing,[86] as well as cancer cell proliferation[90] and asthma.[91] Lastly, miR-126, which is highly expressed in endothelial cells, plays a key role in maintaining vascular integrity and promoting angiogenesis.[92] It is also involved in autoimmune disorders[93] and can be elevated by physical exercise.[93] Therefore, although miRNAs are considered promising biomarkers for certain pathologies, these miRNAs lack specificity and cannot be used to predict the occurrence of leg ulcers in SCD. Additionally, the regulation of miRNA involves both genetic and epigenetic factors. miRNAs interact with redox regulation: Redox changes influence the expression of miRNAs, while miRNAs, in turn, modify the expression of redox regulators,[94] which is particularly relevant in the context of SCD. Isolating haemolysis, oxidative stress or other factors can be challenging when studying leg ulcers because these factors often interact in a complex manner, creating a 'domino' or even a 'vicious cycle' effect.

Oxidative stress

Gene regulators of oxidative stress have been studied in the context of SCD and leg ulcers. Glutathione S-transferases (GSTs) display peroxidase activity and may protect from oxidative damage. GSTs are dimeric units and, based on amino acid sequence, are described in seven classes: alpha, mu, pi, sigma, theta, omega and zeta.[95] The theta category includes GSTT1 and GSTT2 isoforms that exhibit a high activity in human RBCs. The genes encoding the Mu class (GSTM1, GSTM2, GSTM3, GSTM4 and GSTM5) appear to be active in hepatocytes and are known to be highly polymorphic. De Oliveiro Filho et al. showed that patients with a GSTM1 null genotype had a 6.9-fold increased risk of leg ulcers, and patients with a GSTT1 null genotype had a 5.2-fold increased risk of leg ulcers.[96] These findings suggest that oxidative stress probably plays a role in leg ulcer pathophysiology in SCD patients. However, L-carnitine, an antioxidant, did not shorten leg ulcer healing duration in 15 SCD patients.[97] Furthermore, in a controlled trial on the effect of oral zinc sulphate in healing SCD leg ulcers, the healing rate in the treated group was three times faster than in the placebo group.[98] This study was not randomized and thus excluded from the last Cochrane systematic review on interventions for treating SCD leg ulcers.[99] However, since about one-third of SCD patients with leg ulcers have low zinc levels, Eckman proposed that all patients with active or healed ulcers should be supplemented with zinc sulphate at a dose of 220 mg administered orally three times a day.[14] Zinc is an antioxidant that inhibits lipid peroxidation in RBCs, protecting the human body against oxidative stress. In addition, the oxidative stress associated with chronic haemolysis in SCD increases the demand for zinc[100] (Figure 1).

Furthermore, Nolan et al. studied 215 SNPs in more than 100 candidate genes selected for their potential role in SCD pathophysiology.[36] These included genes involved in inflammation, oxidative stress, NO biology, vasoregulation, cell–cell interaction, blood coagulation, haemostasis and growth factors. After considering a false discovery rate of 10%, only one SNP, adjacent to *SMAD7*, remained significantly associated with leg ulcers. SMAD7 is part of the TGF-β pathway. Among its many roles, this pathway impacts cell proliferation, apoptosis, response to tissue injury, endothelial growth, inflammation, immune regulation and extracellular matrix synthesis.[101] Although not firmly demonstrated, the TGF-β pathway could play a role in SCD leg ulcer pathophysiology. However, these results do not currently have any practical application for leg ulcer prediction and treatment.

Factors influencing healing

Genetic factors have been shown to play a role in granulation and epithelialization defects in SCD patients. Overexpression of miR-130a has been associated with chronic venous ulcers and dysregulated re-epithelization processes, granulation tissue formation and wound healing.[102] MiR-130a overexpression was four times higher in SCD patients with ulcers compared to those without ulcers, suggesting miR-130a may play an important role in this complication.[103]

de Carvalho-Siqueira et al. used whole exome sequencing to identify new candidate genes and found only one variant in the *FLG2* gene associated with leg ulcers in SCD patients.[104] This gene has been observed in persistent atopic dermatitis in African Americans and could be involved in leg ulcer development by promoting alterations in the skin barrier. At present, this finding could open a new way of understanding SCD leg ulcer pathophysiology.

At present, there is no published data using the most recent genetic approach, the genome-wide association study (GWAS). GWAS does not require any prior gene selection and allows for the study of exon and intron sequences. GWAS could be useful in identifying or confirming the involvement of genetic factors in leg ulcer mechanisms.

DELAYED HEALING OF SCD ULCERS, MAINLY VENOUS ULCERS

The second part of our review will focus on other common mechanisms shared with venous ulcers, which contribute more to healing delays than to initial ulcer occurrence (Figure 3).

In a French cohort of SCD patients, leg ulcer area < 8 cm^2 (odds ratio (OR) 6.73, 95% CI 2.35–19.31; $p < 0.001$) and duration <9 weeks (OR 3,19, 95% CI 1.16–8.76; $p = 0.024$) were independently associated with wound healing at week 24 in 98 SCD patients. This study highlights that healing is more difficult in older and larger leg ulcers than in recent ones. However, it is unknown whether the natural course of these leg ulcers could have been predicted from ulcer onset or whether the poor healing prognosis results from excessively long delay in initiating treatment. Notably, no association between wound healing and biological markers of haemolysis, HbF or other complications of SCD has been observed.[105]

Venous involvement

Tan et al. observed haemosiderin, an iron storage complex, in the edge of the ulcers of SCD patients. The burden of haemosiderin was between the levels found in ischaemic ulcers and venous ulcers in non-SCD patients. This observation supports the idea that the pathophysiology of SCD ulcers involves both ischaemic and venous components.[106]

Venous insufficiency

We previously highlighted the role of venostasis in the occurrence of leg ulcers in SCD patients. Venous insufficiency is also involved in delaying wound healing. Early observations indicated that bed rest promotes ulcer healing in SCD patients, suggesting that venous hyperpressure may contribute to ulcer healing delay by causing oedema.[5] Venous hyperpressure has been evidenced by Saad and Zago, who measured the clearance (% decrease/min) of ^{99m}Tc, in SCD patients with leg ulcers to demonstrate that their calf muscle blood flow was impaired.[107] Additionally, Billet et al. and Mohan et al. observed rapid refill times using venous pulse recordings, venous plethysmography and laser Doppler flowmetry in SCD patients with leg ulcers compared to those without.[32,108] To better understand the origin of venous hyperpressure, venous incompetency has been studied.

Venous incompetency

Venous hypertension is commonly associated with venous insufficiency, caused by poorly functioning incompetent venous valves. Venous incompetency can be diagnosed using Doppler duplex ultrasound to detect venous. Clare

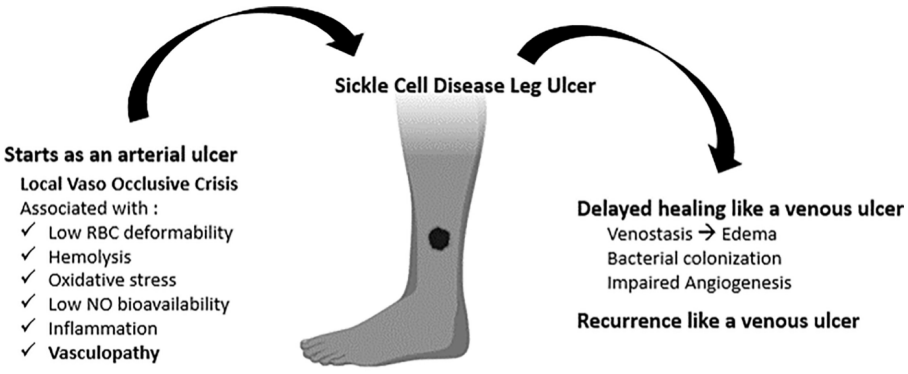

FIGURE 3 Sickle cell disease leg ulcer natural history. Sickle leg ulcer starts as arterial due to sickling, microvascular occlusion and local hypoxia. Once the ulcer is present, venostasis and impaired angiogenesis delay healing.

et al. found an increased risk of leg ulceration in SCD patients with venous incompetency, with a hazard ratio of 2.59 (95% confidence interval (CI): 2.39–2.79, $p < 0.001$).[109] Similarly, Cumming et al. observed a hazard ratio of 4.87 (CI: 2.09–11.03, $p < 0.001$).[9] These data indicate that venous incompetency may contribute to the development of leg ulcers in SCD patients, but is not always present prior to ulcer onset.

Clinical application

Further investigation is required to elucidate the correlation between leg oedema and the onset of leg ulcers. Our proposed explanation is that dysfunction of the local venous and lymphatic systems render them unable to effectively manage the increased blood flow in the ulcerated area, contributing to delayed healing. The application of compression therapy is deemed essential in all SCD patients with leg ulcers, regardless of venous incompetency status.[110] However, the question remains whether routine Doppler duplex ultrasound should be universally adopted for all SCD patients, with and without leg oedema, to screen for venous incompetency. For those SCD patients exhibiting venous incompetency, the implementation of compression therapy could serve as a preventive measure against the development of initial leg ulcers. Nevertheless, encouraging compliance in asymptomatic patients might pose a challenge.

Bacterial colonization

Bacterial colonization of leg ulcer area is an expected phenomenon that does not need to be treated by systematic or local antibiotic therapy, unless signs of local infection are present. Staphylococcus Aureus has been reported to be the most common bacterium present in SCD leg ulcers,[58,111–115] as is the case in other types of ulcers.[115] However, high microbial diversity (driven by aerobes such as Corynebacterium and Alcaligenes, and anaerobes, including Anaerococcus, Peptoniphilus and Porphyromonas) has been shown to delay leg ulcer healing compared to patients with less microbial diversity and a predominance of Staphylococcus Aureus only.[115] On intact skin, Byeon et al. have found elevated ratios of Corynebacterium:Lactobacillus and Staphylococcus:Lactobacillus in SCD individuals with a history of leg ulcers. As no samples were collected before leg ulcer occurrence, these ratios may reflect a susceptibility to leg ulcers or consequences of healed leg ulcers. In addition, the ratio of Lactobacillus: Bacillus was elevated in SCD individuals without a history of leg ulcers. Lactobacillus is involved in a range of protective mechanisms against cutaneous infection or delayed healing, including immune modulation, promotion of re-epithelialization and pathogen clearance.[116] These results, if confirmed in larger studies, could be used to target specific therapy.

Impaired angiogenesis

Nguyen et al. previously investigated wound healing differences in sickle SAD and healthy mice.[117] They found decreased keratinocyte and fibroblast proliferation, and lower numbers of endothelial cells in SAD mice compared to healthy mice. The proliferation and mobilization of bone marrow endothelial progenitor cells were also decreased. Injecting endothelial progenitor cells into the wound shortened the healing process by promoting epidermal cell proliferation and angiogenesis. CXCL12, IL-6, VEGF A, VEGFR-2, Tie-1, Tie-2 and CXCR4 secretion was lower in the wounds of SAD mice compared to healthy mice. Interestingly, the injection of CXCL12 (a chemokine known to promote angiogenesis) also shortened the healing process.[117] This study highlighted the well-known basal vasculopathy and impaired angiogenesis due to alterations in endothelial progenitor recruitment present in SCD. Focusing on this alteration in progenitor recruitment, autologous stem-cell therapy has been tested in 23 SCD patients with leg ulcers with promising results.[118] However, there are no ongoing studies evaluating stem-cell therapy in a larger population.

CONCLUSION

Leg ulcers in SCD constitute a distinct category of chronic wounds with a complex and multifactorial pathophysiology that feature mechanisms commonly observed in both arterial and venous ulcers. Local vaso-occlusive crisis could trigger leg ulceration in vulnerable cutaneous areas due to underlying venostasis. Several factors may modulate the appearance of leg ulcers and healing processes, with genetic factors offering novel research opportunities to improve our understanding of the pathophysiology of this complication.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest disclosure.

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