Leg ulceration in sickle cell disease

KEY WORDS
- Anaemia
- Complications
- Lower limb ulceration
- Rheumatoid arthritis
- Sickle cell disease

Sickle cell disease (SCD) is a relatively rare blood disorder that is characterised by the presence of crescent-shaped — sickled — red blood cells in the bloodstream. These crescent-shaped cells are stiff and sticky and can block blood flow in the small blood vessels of the peripheral blood system, thus preventing the normal flow of nutrition and oxygen. SCD is inherited in an autosomal recessive manner. In this article, Trudie Young gives a comprehensive overview of this medical condition and its link to lower limb ulceration.

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Sickle cell disease (SCD) is an umbrella term that describes a group of inherited health conditions with a disorder of haemoglobin synthesis (Conran et al, 2009). In SCD, the bone marrow produces red blood cells with defective haemoglobin (haemoglobin S); the resulting blood dyscrasia affects multiple organ systems (Trent and Kirsner, 2004; Jones et al, 2013). Until the 1960s, SCD was thought to be mainly a paediatric condition, however, with medical advances many individuals with SCD now reach adulthood (Minniti and Kato, 2016). SCD is the result of a single genetic defect, however, the severity of the disease varies amongst individuals. SCD can be mild and have little impact on individuals' lives, or severe when they suffer from very debilitating complications and an ultimately reduced life span. SCD is a life-long condition; the estimated median survival rate in the UK is 67 years (Sickle Cell Society, 2018).

Herrick first reported leg ulceration in an individual with SCD in 1910. However, it was not until 30 years later that leg ulceration was noted to occur in a definite proportion of SCD (Minniti et al, 2010). Leg ulcers occur ten times more frequently in persons with SCD than in the general population and can commence in the second decade of life (Minniti and Kato, 2016) *(Figure 1)*.

SCD occurs predominantly in individuals of African descent, however, these disorders are also prevalent in the Eastern Mediterranean, the Caribbean and South and Central America. This is thought to be due to areas having a high prevalence of malaria as individuals with SCD have partial protection against malaria and therefore a survival advantage (Sickle Cell Society, 2018). In England, SCD affects approximately 1 in 2,000 live births and there are estimated to be up to 15,000 people living with the disease.

A gene that affects how red blood cells develop causes SCD. If both parents have the gene there is a 1 in 4 chance of a child having the disease. It is possible to not have SCD but to be a carrier of the sickle cell trait. Sickle cell carriers usually have no clinical symptoms and often do not know they are carriers unless they have a specific blood test (Sickle Cell Society, 2018). SCD is often detected at birth by the heel pinprick test, however, symptoms are not present due to the high proportion on intracellular foetal haemoglobin. In all types of sickle cell disease, at least one of the two abnormal genes causes a person's body to make haemoglobin S (HbS). When a person has two haemoglobin S genes (haemoglobin SS), the disease is called sickle cell anaemia, this is the most common and often most severe type of SCD. Early signs of the disease include dactylitis (swelling of hands and feet) and anaemia presenting with tiredness and fatigue (National Heart Lung and Blood Institute [NHLBI], 2014).

There are other haematological causes of leg ulceration such as Polycythaemia rubra vera (Simon et al, 2004).

PATHOPHYSIOLOGY

In SCD, rigid non-liquid protein strands are formed within the red blood cells which alter its shape

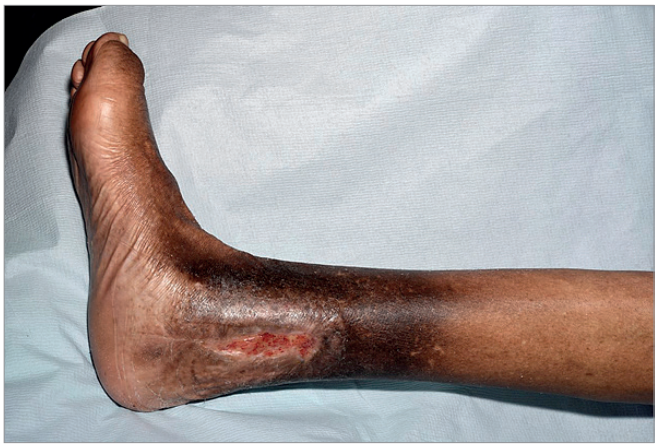

Figure 1. Leg ulcers occur ten times more frequently in persons with SCD than in the general population

into that of a crescent and the cell is then said to be sickled (NHLBI, 2014). The sickled cells become dehydrated, rigid and are less able to negotiate the circulatory system, becoming trapped and lodged *(Figure 2)* within the smaller blood vessels resulting in ischaemia and tissue necrosis (Trent and Kirsner, 2004). SCD was initially thought to be solely related to abnormal haemoglobin (HbS), however, it is now acknowledged that there are many complex mechanisms that form part of the disease process. The primary process is the alteration of the red blood cell producing the defective form of haemoglobin where the morphology of the cell is altered and it has a weakened cell membrane (Conran et al, 2009; Jones et al, 2013). A consequence is occlusion of the vessels and damage to organs supplied by the vessels. The vessel obstruction by sickled cells increases venous and capillary pressure and decreases the oxygen-carrying capacity of the blood (Koshy et al, 1989).

Following an episode of SCD occlusion, the body responds with reperfusion that itself causes tissue damage and an increase in reactive oxygen species and ultimately chronic oxidative stress. The endothelial cells become activated which results in red and white blood cell (mainly leukocyte) adhesion to the wall of the blood vessel which impacts on the occlusion of the vessel. Additionally, in SCD the individuals suffer from an increase in platelet and coagulation activity.

The internal SCD damage produces a chronic inflammatory response confirmed by elevated levels of inflammatory cytokines.

Nitric Oxide (NO) plays a major role in regulating vasodilation and vasoconstriction, thus improving localised blood flow. It also has a role in the moderation of platelets, endothelial cells and leukocytes. NO regulates vascular tone, cell adhesion and blood flow (Jones et al, 2013). In SCD, there is a reduction in the production of NO (Jones et al, 2013). This results in an imbalance between vasoconstriction and vasodilation, favouring vasoconstriction.

The lifespan of normal haemoglobin is 90–120 days, however, in SCD it is much shorter, and death of the red blood cells occurs between days 10–20. This is primarily due to the weakened cell membrane of the sickled cell (Jones et al, 2013). In SCD, two-thirds of haemolysis occurs extravascularly with the remaining one-third of red blood cells haemolyse intravasculary, resulting in anaemia (Kato et al, 2006).

A common complication of SCD, along with anaemia, is a vaso-occlusive pain crisis and during which the haemolytic rate increases even further. Increases in serum LDH and plasma haemoglobin levels are markers of intravascular haemolysis in individuals with SCD (Kato et al, 2006).

Minniti et al (2014) used laser speckle contrast imaging to measure blood flow, infrared thermography to measure tissue temperature and also measured markers of SCD severity, anaemia, the degree of haemolysis and inflammation. The highest blood flow present was in the leg ulcer, progressively less in the immediate peri-wound area and an unaffected control skin area in the same extremity. Microscopic examination showed evidence of venostasis, inflammation and vasculopathy. Blood vessels were increased in number, had activated endothelium, and there was evidence of thrombosis/recanalisation. Consequentially, it is postulated that the high blood flow may be due to chronic inflammation, cutaneous vasodilatation, venostasis and in-situ thrombosis, suggesting that leg ulcers may be another end-organ complication with endothelial dysfunction that appears in patients with SCD at a younger age and with higher frequency than the general population.

SCD COMPLICATIONS

SCD produces a multitude of complications

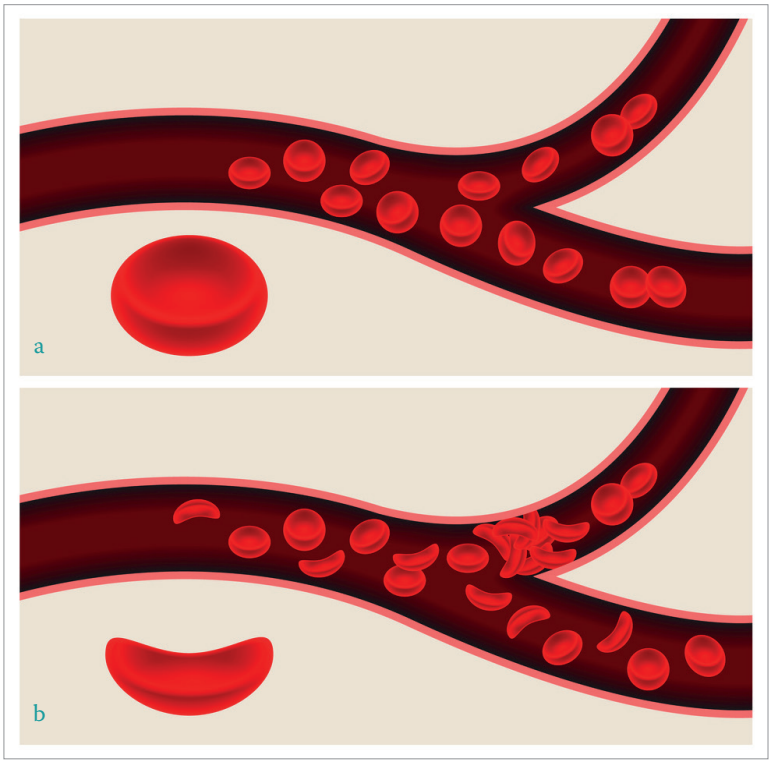

Figure 2. Normal red blood cells flowing freely in a blood vessel (a). Abnormal, sickled red blood cells blocking blood flow in a blood vessel (b)

including pulmonary hypertension, cerebral vascular accidents, priapism and, ultimately, a reduction in the anticipated life span of the individual (Conran et al, 2009; Minniti et al, 2010).

Sickle cell crises are severely painful episodes that can last for up to a week and affect parts of the body e.g. spine, sternum, pelvis and ribs. These crises have individual triggers such as extremes of temperature (NHLBI, 2014).

Individuals with SCD are at risk of serious infections and should protect themselves where possible by vaccination programs (Sickle Cell Society, 2018). Acute chest syndrome is a complication that is characterised by fever and/or respiratory symptoms and can result in respiratory failure (Sickle Cell Society, 2018).

Anaemia is present due to the high rate of haemolysis and inability of the body to make sufficient red blood cells to replace the numbers lost. In these individuals, blood transfusions can be helpful. If individuals had numerous blood transfusions, they may require chelation therapy to reduce the amount of iron in the blood. Transfusion therapy aims to increase the oxygen-carrying capacity of the blood (Sickle Cell Society, 2018).

Avascular or aseptic necrosis of the joints can occur, commonly in the hip joint. It is caused by bone death due to a loss of blood supply to the area (NHLBI, 2014).

Osteomyelitis occurs at all ages in individuals with SCD, it can be difficult to distinguish from vaso-occlusion as both present with pain and localised signs of inflammation, however, the majority of these situations are due to vaso-occlusion rather than infection of the bone. The most common sites for osteomyelitis are the humerus and the femur.

Surgical intervention can pose risks for individuals with SCD, such as acute chest syndrome and acute painful crisis and in certain situations, blood transfusions, oxygen supplementation, prophylactic antibiotic therapy and thromboprophylaxis are recommended (Sickle Cell Society, 2018).

Individuals with SCD and leg ulceration are noted to have increased levels of lactate dehydrogenase, bilirubin and reticulocyte count, which are raised in the presence of haemolysis (Nolan et al, 2006). Leg ulceration is more common in individuals with higher levels of haemolysis. The mechanical obstruction of the circulatory system, high blood viscosity, venous incompetence and hypercoagulability may play a role in ulcer development (Sickle Cell Society, 2018).

SCD can have detrimental effects on the quality of life and mental health of an individual, made worse by chronic leg ulceration (Minniti and Kato, 2016).

The complications of SCD may not occur simultaneously, and screening is required for early detection and treatment (Minniti and Kato, 2016).

CLINICAL PRESENTATION

Koshy et al (1989) completed a prospective study of over 2,000 patients with SCD who were followed up for up to eight years. They found that leg ulceration occurred more often in individuals with lower haemoglobin and foetal haemoglobin levels. Leg ulceration was more frequent in individuals with the more severe form of SCD and in the male gender.

The incidence of leg ulceration in SCD ranges from 25–75% (Trent and Kirsner, 2004).

The ulcers usually present around the medial and lateral malleolus; however, they have also been

found anterior tibia, dorsum and sole of the foot and over the Achilles tendon (Serjeant, 1974; Clare et al, 2002; Jones et al, 2013). There is often a history of localised trauma preceding the ulceration (Minniti and Kato, 2016).

The ulcers have similarities to other ischaemic ulcers in that they are deep with a punched-out appearance (Jones et al, 2013). The ulcers can be small or circumferential on the lower limb. The ulcers produce severe pain, which is unrelated to the size of the ulcer (Minniti and Kato, 2016).

The wound beds may contain slough and necrosis and wound infection is a common event with cases of osteomyelitis reported in the literature (Minniti and Kato, 2016). The surrounding skin may have brown hyperpigmentation and scaling (Trent and Kirsner, 2004).

Due to SCD, the ulcers are often slow to heal, and recurrence is frequent with pain heralding the development of further ulceration (Minniti and Kato, 2016).

People with SCD may also have venous hypertension, therefore, a vascular duplex assessment is required (Jones et al, 2013). Venous incompetence may contribute to the development of sickle cell ulcers (Trent and Kirsner, 2004).

The leg ulceration may be the first sign of end-organ disease in individuals with SCD (Mohan et al, 2000). Minniti and Kato (2016) describe three presentations of leg ulcers:

- The 'one-time' ulcer that occurs during periods of intense physical and/or psychological stress.
- The 'stuttering 'ulcer when individuals have small recurrent ulcers every 6–12 months for many years
- The 'chronic recurrent disabling' ulcer in which the ulcers persist for many years and/or recur in the same or nearby sites.

A biopsy of a sickle cell ulcer is non-specific in determining the diagnosis (Trent and Kirsner, 2004).

TREATMENT

The individual will receive systemic treatments for the disease and its complications, e.g. hypertension.

The Sickle Cell Society (2018) has produced standards of care for adults with SCD in the UK. The standards should be implemented to ensure safe and adequate care if not followed it could result in poor clinical outcomes. The following are the standards relating to leg ulceration.

Annual reviews should include questioning about leg ulceration and inspection of the lower extremities for active or healed leg ulcers.

- Patients with leg ulceration should be treated by a multidisciplinary team, which includes wound care experts.
- Patients with SCD-related leg ulcers should be assessed for venous insufficiency with venous reflux studies.
- Multi-component compression bandaging should be offered, particularly in patients with evidence of venous insufficiency.
- Zinc levels should be measured in patients with leg ulcers and supplements should be offered to those with deficiency

They also gave the following recommendations:

- Education about the prevention and management of leg ulceration should be offered to all patients with SCD
- Patients with SCD-related leg ulcers should be offered appropriate analgesia and may require support from a specialist pain team
- Hydroxycarbamide (Hydroxyurea) should not be withheld from patients with leg ulceration
- A trial of blood transfusion therapy should be considered in patients with intractable leg ulceration,

SCD is a rare illness and leg ulceration is a complication of this disease and as such there are few research trials to provide guidance on leg ulcer management in this patient population (Minniti and Kato, 2016). Therefore, the general principles of wound care should be followed, i.e. debridement, moist wound healing and compression for oedema management (Clare et al, 2002; Martí-Carvajal et al, 2014; Minniti and Kato, 2016).

A Cochrane systematic review on SCD and antibiotic treatment for osteomyelitis did not return any relevant trials on the topic. Whereas an earlier review found evidence to support the use of topical RGD peptide matrix, which reduced ulcer size in treated participants compared to controls (Martí-Carvajal et al, 2019). However, the evidence of efficacy is limited by the generally high presence of bias in the study.

Hydroxyurea is the main drug used to treat SCD and is supported by a Cochrane systematic

"A number of self-help groups exist, providing a veritable plethora of resources. One such group is the Sickle Cell Society"

review (Martí-Carvajal et al, 2014), although it lacked evidence on its long-term benefits (Nevitt et al, 2017). Hydroxyurea has an indirect effect on the vaso-occlusive process by inhibiting the polymerisation of HbS and reduces the sickling process within the red blood cells (Conran et al, 2009). It also decreases haemolysis, the number of leukocytes and inflammatory cytokines whilst increasing haemoglobin. Hydroxyurea therapy aims to maximise the foetal haemoglobin response, which protects HbS (Minniti and Kato, 2016). Hydroxyurea aims to increase the NO production (Jones et al, 2013). It reduces the number of episodes of vaso-occlusive pain crises, acute chest syndrome and anaemia.

Hydroxyurea can cause leg ulceration, however, if stopped the wound should be measured for 6 months and if there is not a 50% reduction in size the hydroxyurea may be restarted (Minni and Kato, 2016). The Sickle Cell Society (2018) state that there is insufficient evidence to stop hydroxyurea in individuals with SCD and leg ulceration. The side effects of hydroxyurea include leukopenia, neutropenia and thrombocytopenia that are mild and reversible with dose reduction or discontinuation of the medication (Sickle Cell Society, 2018).

Opioids are the mainstay for pain relief in leg ulceration associated with SCD (Minniti et al, 2010). Blood transfusions have been postulated to improve leg ulcer healing rates, however, the lack of evidence and complications associated with the treatment means it is difficult to recommend routine transfusions in individuals with SCD and leg ulceration. A trial of transfusion may be of value to individuals with significant anaemia and leg ulceration (Sickle Cell Society, 2018). Red cell transfusions are recommended as an emergency life-saving measure in SCD (Sickle Cell Society, 2018).

Pentoxifylline has been used to treat sickle cell ulcers and is thought to decrease the sickling of the red blood cells, increasing erythrocyte deformability, increasing leukocyte flexibility, inhibiting platelet aggregation, reducing blood viscosity and decreasing plasma fibrinogen levels (Trent and Kirsner, 2004).

Haematopoietic stem cell transplants is a potentially curative option for SCD (Frost and Tredwell, 1990). It is normally reserved for the paediatric population and is not without 'host versus graft' complications. The NHS currently only funds this therapy in the under 19-year-old age group (Sickle Cell Society, 2018).

SCD affects the emotional well-being and economic status of individuals (Frost and Tredwell, 1990) and this was confirmed in a recent Sickle Cell World Assessment Survey (SWAY) of more than 2,000 respondents across 16 countries (Sickle Cell Society, 2019).

Psychological support is necessary for this long-term debilitating condition. Self-help groups exist and provide a veritable plethora of resources, examples of which can be found at https://www.sicklecellsociety.org/.

Sarri et al (2018) completed a systematic literature review and subsequent assessment of patient-reported outcome instruments in SCD. They identified five adult and three paediatric instruments developed for SCD, however, there was insufficient data to assess the validity and reliability of the instruments.

CONCLUSION

Abnormal sickle haemoglobin forms long polymers (chains) within the red blood cells when they become deoxygenated. This damages the red blood cells and makes them stickier, leading to blockages and reduced blood flow causing pain and organ damage. Foetal haemoglobin stops the formation of the polymers and hydroxyurea is used to raise foetal haemoglobin (Nevitt et al, 2017).

Leg ulceration is a recognised complication of SCD, the disease itself and treatments for the disease may hinder and/or help the healing process.

Individuals who suffer from SCD complain of inadequate education of health professionals and inequality of access to health care (Sickle Cell Society, 2018).

The Sickle Cell Society recommends that primary care requirements of individuals with SCD include leg ulcer services (Sickle Cell Society, 2018).

Several potential drug therapies are emerging for SCD including gamma globulin depression, which includes anti-inflammatory agents, vaso-active and anti-adhesive agents.

Leg ulceration is an unwanted complication of SCD that can produce pain, detrimentally affect quality of life and remain non-healing for many

years. There is a lack of specific guidance on leg ulcer management in this patient population. Individuals with SCD have unique care requirements and these should be recognised and accepted by healthcare professionals working in the field of tissue viability.

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