Review

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Review

Exercise in Sickle Cell Disease: The Impact on Pathophysiology and Clinical Symptoms

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Highlights

What are the main findings?

- Numerous studies have reported encouraging safety data for brief periods of high intensity exercise, extended periods of moderate intensity exercise, and regular exercise training programmes conducted over eight to twelve weeks for patients with sickle cell disease.
- Regular physical activity can potentially have a positive impact on numerous underlying pathophysiological processes in sickle cell disease.

What are the implications of the main findings?

- The impact of regular exercise training in sickle cell disease represents an exciting area for future research, with a particular need to investigate how regular physical activity impacts patients' clinical conditions and outcomes.
- Focus should be on identifying an ideal level of exercise that provides maximum benefit for minimum risk and in developing a set of evidence-based generalised exercise guidelines and recommendations for the sickle-cell disease population.

Abstract

Sickle cell disease (SCD) is one of the most common inherited blood disorders worldwide. Clinical manifestations are variable, but include hyposplenism, renal impairment, cardiovascular disease, respiratory complications, and cerebrovascular disease. Frequent painful vaso-occlusive crises, hospitalisations, and other physical and psychological ramifications can have profound effects, including children missing school time resulting in impaired academic performance and adults missing work leading to employment loss. This review examines the possible risks and benefits of exercise in the SCD population. Regular exercise plays an important role in improving physical and mental health, but fears around the potential consequences of exercise for the SCD population are present in children, their families, schools, and other organisations. This can result in children not taking part in as much regular exercise as their peers and being excluded from group activities. Studies have suggested that healthcare professionals are often not discussing possible benefits of physical exercise with patients, likely as there are no guidelines regarding a safe level of activity. An acute increase in inflammation secondary to exercise could increase the risk of vaso-occlusive crises, but regular physical activity is known to play an important role in disrupting chronic inflammation across a wide range of pro-inflammatory diseases. Indeed, studies have demonstrated positive responses to exercise in the SCD population, from improvements in skeletal muscle microvasculature to performance in cardiovascular tests. It is important that recommendations are developed regarding types of exercise and the ideal amount of exercise for maximum benefit with minimum risk in SCD individuals.

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1. Introduction

Sickle cell disease (SCD) is one of the most common inherited blood disorders worldwide. Based on an estimated birth rate of more than 300,000 each year, it is thought that at least three million people are living with the condition[1]. About 75% of these are in sub-Saharan Africa[2]. Clinical manifestations are widespread and variable, but include hyposplenism, renal impairment, cardiovascular disease, respiratory complications, and cerebrovascular disease[3]. Sickle cell disease has a huge impact on the individual's quality of life. Frequent painful vaso-occlusive crises, hospitalisations, and other physical and psychological ramifications can have profound effects, including children missing school time resulting in impaired academic performance[4], and adults missing work leading to employment loss and financial difficulties[5].

2. Sickle Cell Disease Pathophysiology

Sickle cell disease is an autosomal recessive genetic disorder where a single nucleotide mutation (adenine to thymine) in the β-globin gene results in the substitution of valine for glutamic acid and the production of HbS – sickle haemoglobin[6]. Under deoxygenated conditions, haemoglobin polymerisation occurs due to the hydrophobic residue of the valine binding to other hydrophobic residues, causing HbS molecules to aggregate[7]. This polymerisation results in the formation of long branching chains of HbS that can disrupt the architecture and flexibility of the erythrocyte, leading to the formation of characteristic "sickle-shaped" red blood cells which become rigid, fragile, and can obstruct vessels. Cellular dehydration also results, further contributing to the stress on the cell. The polymerisation of haemoglobin resulting in dehydrated sickled erythrocytes leads to two major pathophysiological processes – vaso-occlusion with associated ischaemia-reperfusion injury and intravascular haemolysis and haemolytic anaemia[6]. Over time, this leads to progressive organ damage.

The formation of dehydrated, deformed, and rigid sickled erythrocytes predisposes to the occlusion of post-capillary venules as a result of their interaction with leucocytes and the vascular endothelium. Vaso-occlusion in turn leads to infarction, haemolysis, and inflammation. An increase in inflammation and the levels of pro-inflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α results in endothelial activation and drives increased expression of VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intracellular adhesion molecule-1) and other adhesion molecules. This further increases the tendency of sickled erythrocytes to adhere to the vascular endothelium and precipitate vaso-occlusive events in a vicious cycle[8–11]. Restoration of blood flow to the post-capillary venules then results in reperfusion-mediated injury that generates free radicals and causes oxidative damage, resulting in further inflammation, vasculopathy and endothelial dysfunction.

The haemolytic anaemia seen in SCD is also driven by HbS polymerisation, which results in the formation of sickled erythrocytes that are rigid and fragile. Haemolysis causes anaemia, fatigue, and cholelithiasis[6]. It is also thought to contribute to the development of progressive vasculopathy that is seen in SCD patients. This results in the development of systemic and pulmonary hypertension as patients with sickle cell age[12,13]. The vasculopathy also contributes to the increased risk of cerebrovascular disease, specifically strokes and silent cerebral infarcts[14,15]. An association between the severity of haemolytic anaemia and pulmonary hypertension has been reported in a number of prospective studies of both adults and children with SCD[13,16–19]. In addition, lower steady state haemoglobin concentrations and increased rates of haemolysis have also been found to be associated with certain complications, including cholelithiasis, priapism, and cutaneous leg ulceration. It has been proposed that there are two sub-phenotypes of SCD patients: those with low haemoglobin concentrations and high haemolytic rates that are more likely to develop vasculopathy,

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and those with higher haemoglobin concentrations who appear to be more prone to episodes of acute pain, as well as possibly acute chest syndrome[20].

One key mechanism through which haemolytic anaemia drives endothelial dysfunction is an increase in free haemoglobin in the plasma following its release during intravascular haemolysis. Free plasma haemoglobin, as well as free heme, generate free reactive oxygen species (ROS). ROS damage endothelial cells directly through peroxidation of the lipid membrane and DNA fragmentation, and also strongly bind to nitric oxide (NO)[21–23]. The functional nitric oxide deficiency that results further contributes to the vasculopathy. Nitric oxide is usually produced by the endothelium and plays a key role in regulating basal vasodilator tone. It also inhibits platelet and haemostatic activation[24], as well as the transcriptional expression of nuclear factor κB (NF κB)-dependent adhesion molecules such as VCAM-1, ICAM-1 and the selectins[25]. A reduction in nitric oxide availability will therefore result in increased expression of these adhesion molecules and further play into the vicious cycle by contributing to an increased risk of adhesion between sickled erythrocytes and the endothelium and ultimately an increased risk of vaso-occlusive events. Release of arginase-1 into the plasma as erythrocytes haemolyse also plays a role. Arginase metabolises arginine in the plasma into ornithine and in doing so decreases the required substrate for endothelial NO synthesis. This further contributes to the decreased NO bioavailability seen in SCD[26,27]. Markers of oxidative stress have been found to have a significant association with the loss of microvascular function in children with SCD[28].

Oxidative stress likely also has direct effects on red blood cell (RBC) rheology, which is known to be abnormal in SCD patients[7,29]. Studies on the response of RBCs to oxidative stress have shown a decrease in RBC deformability, a slight decrease in RBC aggregation and a large increase in the strength of RBC aggregates (the sheer stress required to disperse RBC aggregates that have formed)[30,31]. The magnitude of those changes was shown to be two- to three-fold higher in RBCs from SCD patients than controls, suggesting SCD RBCs are more susceptible to the effects of oxidative stress[31]. Decreased RBC deformability has itself been shown to result in a decrease in tissue oxygenation and blood flow in the microcirculation[32,33]. Decreased RBC deformability resulting from increased oxidative stress will also drive a further vicious cycle. There is a clear relationship between RBC deformability and fragility and the extent of haemolysis in SCD[29]. Increased haemolysis will further promote increased oxidative stress, promoting further RBC deformability, and therefore, in turn, further haemolysis. The increase in RBC aggregate strength may also itself disturb blood flow in both the micro- and microcirculation and increase the risk of developing clinical complications[34]. There is an association between increased RBC aggregate strength and acute chest syndrome (ACS) in children with SCD[35], and a rise in both RBC aggregation and RBC aggregate strength has been demonstrated in SCD patients during a vaso-occlusive crisis when compared to a steady state baseline[36].

There is also evidence that haemolytic products, including free plasma haemoglobin and heme, act as erythrocytic DAMPs (danger-associated pattern molecules) and can further contribute to the chronic inflammation and vasculopathy seen in SCD through directly activating innate immune pathways via toll-like receptor 4 (TLR4) and NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome signalling[23,37]. A number of *in vitro* studies and studies in SCD mice have supported an important role for free plasma heme – and its interactions with TLR4. *In vitro*, the incubation of heme with vascular endothelial cells has been shown to induce the expression of adhesion molecules including ICAM-1, VCAM-1, and E-selectin[38], and injection of heme into healthy mice has been shown to result in increased expression of adhesion molecules[39]. Furthermore, it has been shown that giving heme to sickle mice results in lung injuries typical of acute chest syndrome and a decreased survival rate[40]. The role of TLR4 in mediating this heme-related pathophysiology was demonstrated by showing that TLR4 inhibition in chimeric SCD mice were protected from developing ACS when administered heme[40]. In human studies, an association has been found between plasma free heme concentration and the incidence of vaso-occlusive crises

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and ACS in children with SCD[41]. It is also suspected that heme activates the innate immune complement system and stimulates neutrophils to release NETs (neutrophil extracellular traps)[23].

3. Clinical Outcomes

SCD confers a significant burden on patients, with reduced average life expectancy[42] and a significant negative impact on quality of life[43,44]. There is a large variation in the clinical manifestations and outcomes of SCD, which vary from death in childhood to relatively symptom free life into the eighth decade[1]. A large study in the US of over 3500 SCD patients showed that while there was an average of 0.8 significant episodes of pain a year, nearly 40% of patients had no episodes, and just over 5% of patients had between three and ten episodes a year[45]. A study of cerebrovascular disease in over 200 children with SCD showed that 50% of patients have some form of cerebrovascular disease by the age of 14, with the other half showing no evidence of this problem[46]. The extent of this variability remains unexplained.

3.1. Genetic Factors Influencing Outcomes

There is evidence that the maintenance of high fetal haemoglobin (HbF) concentrations after infancy results in a number of clinical benefits, including increased life expectancy[42] and reduced frequency of acute pain[45]. Higher HbF levels reduce intracellular HbS concentrations and interrupt polymerisation. HbF concentration is inherited as a quantitative genetic trait, with a number of major loci identified[47]. The co-inheritance of α-thalassaemia is also thought to modify the phenotype. Co-inheritance of α-thalassaemia reduces the concentration of haemoglobin in each erythrocyte and decreases the tendency of HbS to polymerise. Increased haemoglobin concentrations and decreased rates of haemolysis are seen in these patients[6]. Clinical effects are variable: for example, co-inheritance of α-thalassaemia has been shown to reduce the incidence of cerebral vasculopathy[48–50], but conversely does not reduce pain frequency or maybe even increases it[51]. There is no increase in survival[52].

3.2. Health Inequity, Environmental factors, and Variation in Outcomes

There are discrepancies between outcomes in high resource and low resource settings. For example, 99% of children with SCD in London survive to adulthood[53], compared to less than 50% in Tanzania[54]. Infection is undoubtedly a key environmental factor influencing clinical outcomes for SCD individuals and it is likely the most important cause of premature death in SCD populations in Africa[1]. The potential impact of infection in SCD is influenced by the access to prophylaxis and treatments, which are more readily available in high resource settings[1,55]. The availability of other treatment options also plays a large role in the differences in outcomes seen. Hydroxycarbamide is increasingly available and widely used, but there is a large discrepancy in access to this medication between high resource and low resource settings[1,55]. Hydroxycarbamide reduces vaso-occlusive complications and evidence also suggests it may increase life expectancy[56–58]. In a high-resource setting like the UK, top up or exchange blood transfusions can be used in patients with SCD in emergency situations including acute anaemia or acute chest syndrome (ACS) to both increase oxygen-carrying capacity and decrease vaso-occlusive complications[59]. A number of SCD patients in the UK also receive regular blood transfusions to help manage their symptoms, particularly when hydroxycarbamide has been found to be ineffective or is contraindicated[59]. This presents a stark contrast to many other parts of the world, where patients do not have access to a safe or sustainable blood supply[59]. Other interesting, and potentially even curative, options for treatment exist in the form of allogenic haematopoietic stem cell transplantation or gene therapy, with the gene therapy product exagamglogene autotemcel (exa-cel) being recently approved by the National Institute of Health and Care Excellence (NICE) for use in the UK in 2025, for example[60,61]. However, these treatments are not without significant risks, including those related to the myeloablative conditioning required[62–64]. In addition, even in high-resource settings these treatments have extremely high

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costs and are only available to a very small number of patients with severe disease, with exa-cel being estimated to be used to treat 50 patients a year in the UK[60] and to cost over £1.5 million per course of treatment[61]. Allogenic haematopoietic stem cell transplantation has been found to cost nearly $300,000 in the US[65]. These high costs, as well as a lack of appropriate infrastructure and appropriately trained healthcare professionals, significantly limit access to these options in lower resource settings, further exacerbating health inequities in SCD between high and low resource settings. While allogenic stem cell transplantation and gene therapies represent interesting emerging therapies in SCD, there is and historically has been a relative lack of funding and research into SCD when compared to other diseases with lower global incidence[55,66]. Less funding and less research will ultimately result in relatively fewer new treatments, and this will also influence the health outcomes seen in SCD. Socio-economic factors also play an important role in determining a degree of the variability seen in SCD and contributing to health inequities[67]. Nutrition, the home environment, parental health, and smoking/exposure to second-hand smoke are all likely to influence clinical severity[68,69].

Other environmental factors can influence the clinical outcomes of patients with SCD, such as temperature. SCD patients report cold weather to be a relatively common precipitant of acute pain[70]. Exposure to cold temperatures can cause increased peripheral vasoconstriction, in turn leading to slower blood flow, higher levels of deoxyhaemoglobin and faster rates of HbS polymerisation, thereby resulting in increased rates of vaso-occlusion and pain. The vascular dysfunction that develops in SCD patients, as well as vasomotor hyperresponsiveness, are also felt to contribute[71–73]. The evidence for the impact of temperature, however, is inconsistent. Studies from Jamaica, Ghana, Kuwait, Canada and the USA have found a link between cold or rainy weather and increased episodes of pain in SCD[70,74], whereas other studies conducted in the UK and US, have found that low temperatures do not precipitate pain in SCD[75].

Wind speed has been associated with increased admissions to hospital for acute sickle pain in several studies[75–78]. This could potentially be due to the effects of wind on skin cooling and vasomotor instability. Humidity has also been found to be statistically associated with symptom development in SCD, but the findings are not consistent. For example, higher humidity has been linked to more frequent painful episodes in studies in Kuwait and Canada[76,79], whereas it has been linked to fewer hospital admissions in London[78]. A study in France found both high and low humidity to be associated with increased emergency admissions[74].

Levels of air pollution may also contribute to the clinical variability in the outcomes of SCD. A study in the USA found a significant positive association between pollutants generally indicative of traffic emissions and corresponding emergency department visits[80]. Interestingly, it also found this correlation was stronger amongst paediatric patients. Another USA study found a positive association between short-term (within two weeks) variations in the levels of common air pollutants and hospital encounters in children with SCD[81]. A further study has shown an association between nitrogen dioxide (NO2) exposure and abnormal pulmonary function in children with SCD[82]. Exposure to higher levels of air pollution may contribute to acute and chronic oxidative stress, systemic inflammation and endothelial dysfunction and therefore to the ongoing pathophysiology of SCD[83–86].

4. Exercise and Sickle Cell Disease

Regular aerobic exercise plays a role in sustaining and improving physical and mental health and wellbeing[87,88]. On the contrary, a lack of physical activity increases all-cause mortality and overall poor health[87–91] and is associated with the development of a wide range of chronic health conditions[92]. The role of regular exercise in providing protection against, and potentially treatment for, a wide variety of chronic diseases is increasingly clear. Regular exercise has been demonstrated to have protective effects against cardiovascular disease, type 2 diabetes mellitus, colon cancer, and breast cancer, for example[93].

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Despite this, patients with SCD have historically often felt discouraged from participating in physical activity, whether secondary to their own fears of experiencing a vaso-occlusive crisis[94,95], the fears of their parents or their schools, or the fears of healthcare professionals. This may be due to the lack of guidelines for exercise in this population[96]. Patients with SCD are more likely to be sedentary[97] and have reduced physical fitness with decreased exercised capacity and tolerance compared to healthy controls[98,99]. It has been feared that changes induced by acute exercise, such as acidosis, oxidative stress, and dehydration, may increase the risk of sickling and acute clinical complications. There is, however, a growing body of evidence that moderate intensity exercise training is safe and well tolerated by SCD patients, and may confer a number of health benefits including improved cardiorespiratory function and muscular function[37].

4.1. Reduced Exercise Tolerance

A major contributor to the reduced exercise capacity seen in SCD individuals is chronic anaemia. A small study of ten patients with SCD has shown that a single partial exchange transfusion can improve exercise capacity of SCD patients[100]. This may be in part due to the increase in haemoglobin, but other factors must be contributing as large increases in exercise capacity were seen for relatively modest improvements in haemoglobin. Furthermore, two of the patients had a reduction in haemoglobin levels following the transfusion but were still found to have their exercise capacity improve. In addition to anaemia, abnormal blood rheology is likely to play a role in reduced exercise tolerance in SCD patients. RBC deformability has been demonstrated to be an independent predictor of 6-minute walking test performance in children with SCD, alongside haemoglobin levels[101].

Cardiac dysfunction is also likely to play a role in the reduced exercise capacity seen in the SCD population. Chronic anaemia leads to an increase in cardiac output secondary to increases in left ventricular stroke volume, with only minimal increases in heart rate, and this results in significant dilation of the left ventricle[102]. Over time, this progressive dilation results in increased wall stress, increased left ventricular mass and diastolic dysfunction. Diastolic dysfunction has been shown to be common in children with SCD[103,104], and to correlate with reduced exercise tolerance[105,106]. The degree of diastolic dysfunction is independently associated with early increases in blood lactate concentrations during exercise[107]. Earlier increases in blood lactate for a given work rate and oxygen consumption (VO2) suggest lower physical fitness.

SCD is also associated with pulmonary dysfunction. Lung function abnormalities are frequently noted in children and adolescents with SCD and lung function declines with increasing age[108,109]. Pulmonary hypertension is a serious and common complication of SCD, seen more in the adult than the paediatric population[110,111]. A history of recurrent ACS and restrictive lung disease has been associated with reduced exercise capacity and impaired performance in a 6-minute walking test in children and young adults with SCD[112]. Gas-exchange data obtained from cardiopulmonary exercise testing (CPET) in children and adults with SCD shows impaired O2 uptake, reduced ventilatory efficiency, and a lower O2 pulse (the amount of oxygen consumed per heartbeat) during exercise when compared to healthy controls[99,113–115].

Muscular dysfunction also plays a role in contributing to limited aerobic capacity in SCD, as well as decreased anaerobic capacity and muscle strength[98,116,117]. Patients with SCD show skeletal muscle hypotrophy[118–120], and histological analysis reveals reduced capillary density and decreased capillary tortuosity[119,120]. Skeletal muscle in SCD patients has also been found to display impaired oxidative capacities, with lower oxidative enzyme activity than healthy controls[118,119]. This lower oxidative capacity leads to an earlier favouring of non-oxidative glycolysis and an earlier accumulation of lactate during exercise in SCD patients[114,121,122]. It is unclear to what degree these changes are direct pathophysiological consequences of SCD versus deconditioning secondary to the decreased level of physical activity seen in individuals with SCD when compared to healthy controls[97,123].

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4.2. Concerns Regarding Acute Exercise

The concerns around acute exercise in SCD have largely centred around fears that it will increase the risk of sickling and hence the risk of vaso-occlusive crises, particularly at high intensities. Exertion has frequently been noted as a potential precipitant of vaso-occlusive crises in patient-reported questionnaires[124]. For example, one study found that 30% of patients presenting to the emergency department with a severe vaso-occlusive crisis requiring hospitalisation reported exertion as a precipitating factor[125].

Acutely, exercise results in an inflammatory response characterised by the mobilisation of leukocytes and increased levels of circulating inflammatory mediators[126,127]. The exact form of inflammation varies according to the type, intensity, and duration of any exercise, as well as the relative fitness of the participant. SCD causes chronic inflammation, with raised pro-inflammatory mediators (including IL-1, IL-6, IL-8, and TNFα) found at rest in SCD patients when compared to healthy controls[11,128–130]. Given the role inflammation plays in the pathophysiology of SCD and the already higher baseline inflammatory state in these patients, further increases in the level of inflammation during and immediately following an acute bout of exercise could further drive the expression of vascular endothelial adhesion molecules and further increase the risk of sickled RBCs adhering to the endothelium and precipitating vaso-occlusive events. Indeed, intense exercise in healthy individuals has been shown to increase levels of endothelial adhesion molecules including ICAM-1, VCAM-1, and some selectins[131].

During moderate to intense exercise, there is a reduction in pH due to the production of lactic acid by anaerobic respiration. This decreases the affinity of haemoglobin to oxygen through the Bohr effect which is usually beneficial to facilitate the delivery of oxygen to the tissues. In the context of SCD, however, the increased deoxygenation could precipitate HbS polymerisation and a vaso-occlusive event[37]. Acidosis has been shown to also be an independent risk factor for HbS polyermisation, even outside of the impact of the Bohr effect, thought to be secondary to the activation of several RBC cationic channels leading to a reduction in intracellular water content and therefore an increase in HbS concentration[34,132]. Further to this, a decrease in blood pH has also been shown to result in an increase in blood viscosity[133]. This will also increase the risk of vaso-occlusive events, independently of the effects of acidosis on HbS polymerisation and RBC sickling. *In vitro*, studies have shown that acidosis is a strong promoter of HbS polymerisation and therefore RBC sickling. The relative amount of sickled RBCs has been shown to increase markedly from 1% at a pH of 7.4 to >90% at a pH of 7.0[132]. *In vivo* studies have also supported that blood acidosis is a strong potential triggering factor for RBC sickling and painful vaso-occlusive crisis[132]. The extent of exercise-induced intramuscular acidosis may be higher in SCD patients, supported by results in mouse models of SCD[134], as well as findings that SCD patients are prone to early lactate accumulation when exercising[114,121]. Taken together, this could suggest that acidotic conditions during exercise could drive HbS sickling and ultimately vaso-occlusive events in patients with SCD.

Increases in temperature that occur during exercise could further decrease HbS affinity to oxygen and also contribute to an increased risk of sickling[37]. Dehydration occurring during exercise could also transiently result in an increased haematocrit and blood viscosity, potentially also promoting vaso-occlusive complications[34]. Increases in adrenaline secondary to acute exercise could also contribute to an increased risk of vaso-occlusion. Adrenaline impacts microvascular blood flow and increases the adhesion of sickle RBCs to the vascular endothelium[135,136].

Results from some studies have suggested that a proportion of SCD patients may be at risk of exercise-induced haemoglobin desaturation, even during mild exercise such as in a 6-minute walking test[137]. The incidence of this amongst paediatric SCD populations has been found to vary from 8%[138] to 42%[139]. This raises concern, as if the haemoglobin desaturation during mild to moderate exercise is significant, it could promote HbS polymerisation and sickling.

Acute exercise also increases the generation of superoxide anions and O2-derived intermediates[140]. In addition to damage to the vascular endothelium and increased inflammation,

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accumulation of reactive oxygen species (ROS) may also directly damage RBCs in SCD patients and further reduce RBC deformability[31].

The impact of acute exercise on blood rheology is another potential concern. Blood rheology is abnormal at baseline in patients with SCD, with a reduction in RBC deformability, increased strength of RBC aggregates, increased plasma viscosity, and increased blood viscosity for a given haematocrit compared to healthy controls[36,141]. Acute exercise increases blood and plasma viscosities, results in a rise in haematocrit, increases RBC aggregation, and decreases RBC deformability, particularly when effort is intense[34,141]. Increased blood viscosity is usually well tolerated in healthy individuals, but this is not the case in SCD patients due to microvascular dysfunction[34,142]. Increased blood viscosity has been found to be an independent risk factor for frequent vaso-occlusive crises in children with SCD[34,35,142]. Thus, the changes seen during acute exercise could increase the risk of vaso-occlusive crisis.

4.3. Single Acute Bouts of Exercise May Be Safe and Well-Tolerated

Numerous studies have investigated the impact of single acute bouts of moderate intensity exercise in both children and adults with SCD[143–146]. Overall, the results of these studies suggest that a single bout of moderate intensity endurance exercise is not associated with major changes in RBC deformability, blood viscosity, inflammation, or oxidative stress. The studies also suggest that this type of exercise is safe in patients with SCD, with no clinical complications or vaso-occlusive crises reported.

Safety data from studies from children and adults with SCD also suggests that exercising with increasing intensity until exhaustion, such as during maximal cardiopulmonary exercise testing (CPET) exercise testing, appears to be safe and does not result in adverse events[96,128]. In addition, it has been shown that, while baseline levels of inflammatory biomarkers are higher in SCD patients, the magnitude of the acute inflammatory response to maximal CPET is no greater in SCD patients than in healthy controls[96,128]. A systematic review into the safety of maximal CPET in individuals with SCD included data from nearly 1000 children and adults[147]. The review concluded that maximal-symptom limited CPET was safe for individuals with SCD. Less than 4% of patients exhibited any adverse events: 2% showed electrocardiogram (ECG) abnormalities, 0.1% pain requiring hospitalisation, 0.3% pain without hospitalisation, and 1.1% exercise-induced hypoxia. It is likely that CPET is safe in SCD patients, despite its high intensity, due to the relatively short duration, with the incremental phase of testing usually lasting around 10 minutes in total[148]. It is also only towards the end of the incremental phase that exercise intensity will be higher or maximal, with a gradual ramping up of intensity utilised. CPET protocols also include periods of warming up (the unloaded phase) and cooling down (the recovery phase) that likely contribute to its safety[148]. Studies assessing the impact of higher intensity exercise over longer durations have not been conducted in patients with SCD, likely secondary to fears it would result in acute complications.

4.4. Benefits of Moderate Intensity Aerobic Exercise Training Programmes

In mouse models of sickle cell disease an eight-week training programme has demonstrated improvements in inflammation, blood viscosity, and oxidative stress[149–152]. There have been further investigations into the effects of regular exercise for patients with SCD[95,153–162]. All exercise programmes lasted between 6 and 12 weeks, with two to three exercise sessions per week. A number of studies had participants take part in cycling exercise[95,153,155,157], with some of these studies targeting an exercise intensity equivalent to a blood lactate concentration of 2.5mmol/L (the first lactate threshold, LT1) while others targeted an intensity equivalent to either 70% or 100% of the first ventilatory threshold (VT1). Other studies have investigated aerobic exercise programmes involving a combination of walking, calisthenics, and flexibility exercises[154,158,159]. Importantly, the different training sessions were all found to be safe and well-tolerated, with no clinical complications or adverse events reported. A number of beneficial effects have also been identified, including increased aerobic physical fitness and ventilatory efficiency, increased plasma NO,

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increased muscle capillary density, improved muscle aerobic energetic capacity, and improved scores on standardised measures of quality of life[37,95,153–162]. It is important, however, to note that the studies had relatively small sample sizes and the various exercise programmes have either been conducted entirely supervised in laboratory settings, or been guided by initial supervised laboratory-performed exercise testing, which will limit the generalisability to other settings.

A recently conducted study investigated the impact of eight weeks of increased daily step count in SCD patients in Dakar[163]. A key difference from previous studies was that the intervention was simple: an increase in daily step count either by 25% above baseline for 8 weeks, or by 25% above baseline for 4 weeks, and then 50% above baseline for a further 4 weeks. Increasing step count is easy to perform and can be conducted without medical supervision or prior exercise testing. The results of the study suggest that eight weeks of increasing step count by 25-50% is sufficient to increase physical capacity, decrease pain frequency and intensity, improve vascular function, and decrease inflammation in patients with SCD. There were some limitations to the study, most notably that it did not include any women. Further studies are required in different settings where sedentary behaviour is more common and baseline step counts may be lower.

5. Regular Exercise, Improved Aerobic Fitness, and the Potential Impact on the Pathophysiology of Sickle Cell Disease

5.1. Inflammation

Regular exercise is known to decrease inflammation in healthy individuals[164–167] and has also been associated with long-term anti-inflammatory effects in various chronic diseases[93,168–171]. Exercise may have anti-inflammatory effects through the release of IL-6 from contracting skeletal muscle[172]. Acting as a myokine, IL-6 is thought to drive increased levels of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1ra), as well as decreased levels of TNF-α[93,170]. In a mouse model of SCD it has been shown that eight weeks of aerobic training resulted in decreased levels of several markers of systemic inflammation, including white blood cell count and IL-1β[150], suggesting that regular physical activity in SCD may result in reduced inflammation. Indeed, decreased IL-6 and TNF-α levels have been found in SCD patients following a 12-week exercise programme[161], and decreased IL-6, TNF-α, and IFN-γ levels were found in SCD patients that had increased their step count for an 8-week period when compared to a control group, although there was some variation in results between the study's two different intervention groups[163].

Given elevation of IL-6 in the steady state is associated with an impaired immune response and increased morbidity[130], long-term decreases in IL-6 secondary to regular exercise could be of clinical benefit in patients with SCD. Indeed, studies have suggested that, in general, a profile of low IL-10 but high IL-6 and TNFα is seen in patients who have more frequent vaso-occlusive crises, whereas the inverse (high IL-10, lower IL-6 and TNFα) is seen in patients who have not had a vaso-occlusive crisis in the last nine months[173]. Other studies have provided further support for the benefit of a low IL-6 and high IL-10 environment. A study in adult SCD patients has shown negative correlations between IL-6 values and both the distance walked on a treadmill and estimated peak VO2 values[158]. Reduced levels of IL-10 have been found to be correlated with the frequency, severity, and duration of vaso-occlusive crises in SCD patients[129]. Regular physical activity has been shown to result in markedly increased IL-10 levels in the context of other chronic diseases such as type 2 diabetes mellitus (following a 6 month exercise training programme)[170,174] as well as in post-myocardial infarction patients (following an 8-week exercise training programme)[175]. If regular exercise can result in a favourable shift in these inflammatory mediators in patients with SCD, driving a decrease in IL-6 and an increase in IL-10, it may reduce the frequency of vaso-occlusive events and, ultimately, the clinical burden of the disease.

Increased levels of anti-inflammatory cytokines driven by exercise are also suspected to drive downregulation of TLR4 expression on innate immune cells[169,176]. In healthy individuals of

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different ages, a 12-week exercise programme has been shown to result in a significant reduction in TLR4 expression[177]. Reduced TLR4 expression may well have a clinical benefit: TLR4-mediated signalling is felt to drive inflammation and vasculopathy in response to haemolytic products released into the blood[23,37]. In mouse models of SCD, pharmacological inhibition or genetic knockdown of TLR4 has demonstrated protective effects against the development of ACS following heme administration[178–180]. Decreased expression of TLR4 following regular physical exercise could well attenuate this element of SCD pathophysiology and contribute to reduced inflammation and reduced vasculopathy.

Visceral fat loss secondary to regular physical activity also plays a role in the anti-inflammatory effect seen. Visceral adipose tissue is known to produce a number of inflammatory adipokines including TNF-α, IL-6, and IL-18[170], and excessive visceral adipose tissue is also thought to result in a reduction of plasma anti-inflammatory mediators, together contributing to a chronic low-grade inflammatory state[169,170].

5.2. Vascular Dysfunction, Endothelial Activation, and Cell Adhesion

Regular physical activity has also been shown to have beneficial effects on endothelial activation. Cross-sectional studies have shown that levels of physical activity negatively correlate with endothelial activation in healthy individuals[181,182]. Further, ageing-related increases in plasma sICAM-1 have been shown to be attenuated by regular physical activity[183]. In patients with other chronic conditions such as heart failure, peripheral arterial disease, or type 2 diabetes mellitus, regular physical activity has been shown to result in lower levels of sVCAM-1[171], sICAM-1[184,185], sP-selectin[184,186], and sE-selectin[185]. This process may be mediated by the rise in IL-10 seen following regular exercise[170,174,175], with IL-10 known to downregulate the expression of both VCAM-1 and ICAM-1[187].

Studies with mouse models of SCD have also supported a role for regular physical activity in reducing endothelial activation and dysfunction. Sedentary sickle mice exposed to hypoxia/reoxygenation stress show increased levels of pulmonary VCAM-1[188]. In comparison, sickle mice that had undergone eight weeks of voluntary wheel running did not show this same increase in pulmonary VCAM-1 levels[189]. This suggests that regular physical activity can reduce endothelial activation and improve vascular function in SCD.

Human studies have so far mostly focused on acute bouts of exercise rather than regular exercise training and have yielded differing results. A study in the Ivory Coast measured markers of endothelial activation in 11 SCD patients following 20 minutes of cycling exercise and found a slight increase in sVCAM-1 in both SCD and control groups, and a slight increase in sICAM-1 in just the SCD group[145]. In contrast, a study in the US in 90 children and adolescents who underwent maximal exercise testing found that SCA patients had a higher level of sVCAM-1 at baseline compared to healthy controls, but that the exercise did not induce any further rise[128]. A lower fitness level, defined by peak oxygen consumption (VO2), was independently associated with a greater acute phase response to exercise for sVCAM-1 across SCA patients and healthy controls.

A recent cross-sectional study of 98 adults with SCD in Senegal found an association between higher daily step count and improved vascular function in adults with SCD[190]. Vascular function was assessed using carotid-femoral and carotid-radial pulse wave velocity (CF-PWV and CR-PWV) as a proxy measure for arterial stiffness. A recent interventional study investigating the impact of eight weeks of increased step count in SCD patients looked at vascular function as an endpoint[163]. CF-PWV and CR-PWV decreased in both intervention groups and there was a significant negative correlation between changes in 6-minute walking distance and decreased CF-PWV. In addition, the percentage of HUVECs (human umbilical vein endothelial cells) positive for ICAM-1 after incubation with patient plasma was significantly decreased in the second intervention group, suggesting reduced endothelial activation.

Further *in vivo* studies exploring the impact of longer-term regular physical activity on endothelial activation and the expression of these adhesion molecules in SCD patients are required

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to see whether the promising results seen in other populations with different chronic diseases can be replicated.

5.3. Blood Rheology

Regular physical activity in the general population has been found to result in a number of changes in blood rheology, including an improvement in RBC deformability[191–193] and a decrease in blood viscosity[193–196]. A study in a mouse model of SCD has shown that mice that undertook regular physical activity had a decrease in blood viscosity compared to their sedentary counterparts[151]. Human studies on the impact of exercise on blood rheology in sickle cell patients have so far focused on single acute bouts of exercise. One study found blood viscosity and haematocrit were unchanged compared to resting level in SCD patients following a 20-minute symptom-limited exercise test on an ergocycle, although a mild increase in the percentage of dense sickled RBCs was seen[144]. Another study has demonstrated there was no further alteration in RBC deformability from baseline in SCD patients following 10-12 minutes of submaximal acute exercise on an ergocycle[143]. The same study also subsequently found that the strength of RBC aggregates was decreased in samples taken two and three days after exercise. This may well be of clinical benefit: the strength of RBC aggregates has been associated with the risk of acute chest syndrome (ACS)[35]. A recent cross-sectional study of adults with SCD in Senegal, cited above for its findings regarding vascular function, has also found an association between higher daily step counts and reduced blood viscosity[190]. Future interventional studies should be conducted to explore the impact of regular exercise training programmes on blood rheology in SCD patients.

5.4. NO Metabolism and Oxidative Stress

Regular physical activity, over a period of weeks or months, has been shown to result in upregulation of endothelial NO bioactivity[197] and increased NO bioavailabilty[198]. Studies have also shown that RBCs themselves are able to produce NO[199], as well as that regular physical activity increases the activity of RBC endothelial-like NO synthase (NOS), resulting in an improvement in vascular reactivity[192]. Other potentially beneficial effects resulting from regular physical activity, seen in healthy populations and in individuals with cardiac disease, include a decreased expression of ROS-forming enzymes and enhanced endogenous antioxidant defences, for example upregulation of the activity of RBC catalase and glutathione reductase[170,198,200,201]. A favourable shift in inflammatory profile following regular exercise, including a rise in IL-10, may also play a role in the benefits seen, with IL-10 having been demonstrated to suppress the production of ROS[202,203].

Studies conducted with mouse models of SCD have shown promising results with regards to the impact of regular exercise on NO metabolism. Eight weeks of voluntary exercise training has been shown to decrease oxidative stress, with increased NO production, endothelial NOS (eNOS) mRNA expression, and eNOS activation all found to be increased in the lungs of exercised mice compared to sedentary controls following hypoxia/reoxygenation stress[149].

Studies conducted in the SCD population have focused on acute bouts of exercise. Comparison of SCD patients and healthy controls who performed an acute submaximal exercise test found that the RBC NO level was higher in SCA patients at rest and decreased significantly after exercise, and that free radical levels, while higher in SCA patients at rest, were not affected by exercise[146]. Markers of oxidative stress in 11 SCA patients following an acute bout of moderate endurance exercise (20 minutes of cycling) were found to be unchanged[145]. Thirty minutes of moderate intensity exercise conducted over three consecutive days in SCD patients has also been found to result in a rise in plasma NO[204]. A study investigating the impact of a six-week exercise training programme involving cycling in SCD patients found evidence for reduced nitrosative stress and improved NO bioavailability following the exercise training[95]. The same study also found that plasma free haemoglobin concentration was reduced following the exercise programme, with plasma free haemoglobin known to play an important role in the pathophysiology of SCD through

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generating ROS as well as scavenging NO and creating a functional NO deficiency[21–23]. Overall, the results of these studies suggest that acute exercise does not result in a deleterious increase in oxidative stress in SCD patients. Further studies are required to confirm the effects of longer-term regular physical activity on NO metabolism and oxidative stress.

5.5. Cardiac Effects

Regular physical activity is beneficial for cardiovascular health[205]. Studies have shown that exercise-trained individuals have improved systolic and diastolic function, including a faster diastolic filling rate and a faster left ventricular emptying rate[206]. Beneficial effects on cardiac function have also been demonstrated in SCD patients. A study on the impact of an eight-week exercise programme in 27 adults with SCD demonstrated significant improvement in cardiovascular results following the exercise programme, including an increased ejection fraction and an improvement of diastolic function[154]. Another study investigating the impact of an eight-week exercise programme in SCD patients also demonstrated an improvement in systolic function in the exercise group, with an improved ejection fraction[158]. The authors suggested that this may be related to a reduction in afterload secondary to improved endothelial function, with a similar mechanism having been suggested to be responsible for similar benefits seen in patients with heart failure[207]. Increased NO production may underlie this process and has been seen in studies investigating the effects of regular physical activity in patients with heart failure[208]. Providing further support for this as a potential mechanism of improvement in endothelial function following exercise, increased NO levels have been seen in SCD patients following participation in moderate-intensity exercise protocols[204].

Diastolic dysfunction has been shown to be an independent risk factor for death in SCD patients[209]. If regular exercise can lead to an improvement in cardiac function, this could improve health and decrease mortality.

5.6. Respiratory Function

Regular exercise training has been shown to result in improvements in pulmonary function in patients with chronic respiratory diseases, such as improved gas exchange, decreased respiratory symptoms, and improved functional capacity[210,211]. A large cohort study of UK Biobank participants found higher levels of physical activity are associated with a slower decline in lung function with age in the general population[212]. Given lung function abnormalities are frequently seen in children and adolescents with SCD and decline with increasing age[108,109], such a slowing in decline could be very beneficial.

There are relatively few studies investigating the impact of regular exercise on the pulmonary function in SCD patients. Regular exercise training for six to eight weeks in SCD patients has been found to result in an increase in ventilatory efficiency[95], as well as in a lower respiratory frequency for a given submaximal power output, suggesting improved ventilatory function[118]. A significant improvement in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) has also been found following a 12-week exercise programme in SCD patients[159]. MIP and MEP have been found to be below predicted values in patients with SCD at baseline[213].

5.7. Muscle Structure and Function

In healthy individuals, regular endurance exercise training results in improved type I muscle fibre cross-sectional area and improved oxidative enzyme activities[118], as well as microvascular benefits[153]. Endurance training has been shown to reduce exercise-induced intramuscular acidosis and improve muscle function in a mouse model of SCD[214]. Markers of oxidative stress in muscle tissue have also been shown to be reduced following exercise training in sickle mice[152,214].

In human studies, an eight-week exercise programme in SCD patients resulted in a gain of skeletal muscle microvasculature[153], as well as increased type I muscle fibre surface area and

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increased oxidative enzyme activity[118]. Alongside these histological changes, improved exercise capacity, lower blood lactate concentration, and lower ratings of perceived exertion were also seen in the patients who underwent the training programme. A significant improvement in both handgrip and quadricep strength following a 12-week exercise training programme has also been demonstrated in SCD patients[159]. These results suggest that moderate intensity regular exercise can partially reverse the microvascular and muscular deficits commonly observed in the skeletal muscle of SCD patients, with a corresponding functional improvement also suggested.

5.8. Impact on Clinical Symptoms

The results obtained from various studies investigating the impact of regular exercise programmes in SCD patients is encouraging, but evidence tying the potential improvements seen in various underlying factors such as inflammation or vascular function to improvements in clinical condition is more limited at present.

Some studies have suggested that improved conditioning and physical fitness may result in an improvement in the quality of life of patients with SCD. Following exercise training, SCD patients had a lower rating of perceived exertion for a given submaximal power output[118] and had significant improvements in functional capacity, especially for exercise levels close to those needed for daily activities[157]. The daily activity level of the children and adolescents has been measured both before a period of exercise training and one year after and been found to be increased in 80% of cases[95]. Improved physical fitness may improve quality of life by making it easier for patients with SCD to comfortably perform activities of daily living requiring mild to moderate physical activity. A cross-sectional study conducted in Senegal has found higher daily step counts to be correlated with lower pain frequency and intensity in SCD patients, but not with the frequency of vaso-occlusive crises[190,215]. In addition, the frequency of pain, mean pain intensity, and the degree of interference with daily activities, when assessed using a standardised questionnaire, have all been found to decrease following eight weeks of increased daily step count in SCD patients[163]. Other studies involving eight-week exercise training programmes in SCD patients have shown significant improvements in the scores on standardised quality of life metrics (the 36-Item Short Form Survey, SF-36) in the groups that undertook the exercise programme[158,159].

Future studies should focus on whether regular exercise training results in associated measurable clinical improvement for SCD patients. More studies are required to demonstrate an impact on pain intensity and frequency, as well as on quality of life. No longitudinal or interventional studies to date have investigated whether regular exercise results in a decrease in the frequency of vaso-occlusive crises.

6. Exercise Recommendations in SCD

Clear generalised guidelines for exercise in the SCD population would be of benefit for patients, their families, and clinicians. They should detail how much exercise is safe, what types of exercise are safe, and what precautions should be taken around exercise. Such guidelines do not yet exist.

Guidance on the intensity and duration of exercise that is able to be conducted safely will be a key part of any generalised exercise guidelines. Further work is required to identify the exercise intensity that provides the maximum benefit for the minimum risk in the SCD population. There is a dose-response relationship between exercise and health outcomes, with physical activity above the minimum recommended amounts resulting in more significant improvements, but extremely high intensity exercise, or exercise without appropriate resting periods, being associated with adverse events[127,170]. Many of the studies conducted investigating regular exercise training in SCD patients to date have used baseline exercise testing, such as CPET, to help determine a safe level of exercise. In lower resource settings in particular, access to formal exercise testing is likely to be much more limited. Generalised guidelines should therefore detail forms and intensities of exercise that can be safely practiced in situations where formal exercise testing cannot be conducted. In the absence of specific CPET data, individual differences in disease severities, as well as any individual history of

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exercise-related symptoms or adverse events, should be taken into account when determining what intensity of exercise can be safely targeted. Simpler tests, such as a six-minute walking test, can also be utilised to obtain some general information on exercise capacity. CPET testing and resulting personalised exercise calibration can still play a role where it is available, and the extra information obtained may allow for relatively higher intensities of exercise to be able to be deemed safe, particularly in patients with more severe disease and lower levels of physical fitness where extra caution will be required.

Generalised guidelines will also need to advise on what forms of exercise are safe and can be recommended to SCD patients. Based on the studies conducted so far, it appears moderate intensity cycling, walking, calisthenic exercises, and resistance training can be practiced safely[37]. The potential safety of team sports is another consideration. Team sports increase the opportunity for social interactions, and studies have shown that there are particular mental health benefits seen following participation in organised team sports that are either not as pronounced or not seen at all with participation in individually performed exercise[216,217]. Potential benefits need to be weighed against potential risks, for example the risk of abdominal impacts in contact sports and potential rupture of an enlarged spleen[37]. A pilot study in the Netherlands had eight children with SCD between the ages of 7 and 12 participate in a 10-week programme involving playing football (soccer) and other football-related activities for 90 minutes, and found this form of moderate-to-vigorous intensity organised team sport was safe, with no adverse events or vaso-occlusive crises related to the exercise occurring[218]. Regular water breaks and additional short breaks as required were implemented throughout. Importantly, it also appears that the children in the study enjoyed themselves. At baseline, none of them participated in any organised sports activities. Following the conclusion of the study, every single participant either continued participating in the same training programme or an alternative similar organised sports activity. This will not be the case for all potential training programmes. A study of a home exercise programme in the US found decreased adherence to their exercise programme in the second part of their study, with some of the adolescents involved expressing decreased interest and motivation[155]. Continued motivation and adherence to an exercise programme over a longer period will be vital to ensure continued health benefits and is a factor that future guidelines should consider.

Advice should also be given on important precautions to take during exercise for SCD patients, such as frequent hydration, which will help limit rises in blood viscosity and core body temperature during exercise[34,37,219]. Appropriate periods of warming up and cooling down either side of exercise are also likely to be important in the SCD population[37], and this should similarly be reflected in the guidance provided.

Guidelines should also consider the impact of various environmental factors on the safety of exercise in the SCD population. Training programmes studied so far have largely been conducted either in the laboratory or at home, and it is not known to what extent climatic factors may influence safety. For example, cold temperatures are commonly reported by patients to be a precipitant of acute pain[70] and hot temperatures may lead to an increased risk of dehydration and cardiac strain[37]. Further studies are required to determine the degree to which different temperatures might impact exercise safety, as well as the degree to which any risks can be alleviated by sensible precautions being taken, such as the use of appropriate clothing and appropriate hydration strategies. Exercise conducted outside in urban areas may also result in increased exposure to air pollution, which has been linked to adverse effects including increased hospital visits and abnormal pulmonary function in SCD patients[80–82]. The majority of the published data appears to support a beneficial effect of exercise even at higher air pollution levels, such as levels of fine particulate matter with a diameter less than 2.5 micrometres (PM2.5) or levels of coarse particulate matter with a diameter less than 10 micrometres (PM10) above the 70th percentile for exposure in a study in South Korea (PM2.5 >27.86μg/m^3 and PM10 >55.13μg/m^3)[220] or above the median concentration seen across a five-year period in another study in Sweden, where average pollution levels are relatively lower (PM2.5

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>5.7μg/m^3 and PM10 >9.6μg/m^3)[221,222]. Further research into this area is needed with a particular focus on investigating the effects of exercising in polluted air in both children and patients with SCD.

7. Conclusions and Future Directions

Regular exercise training can potentially positively impact on pathophysiological processes underlying sickling and vaso-occlusion in patients with SCD. In addition, it can result in improvements in cardiopulmonary and muscular function and potentially in quality of life. Importantly, and in contrast to other potential interventions, regular exercise has no or at least relatively limited cost and is easily generalisable across different populations.

Future studies should investigate whether regular exercise training in SCD patients results in decreased pain and a reduction in the frequency of presentations to hospital with vaso-occlusive events. Another area of future focus should be on evaluating the impact of exercise regimens that are easy to implement and can be widely introduced, including in lower resource settings. A key focus should be aiming to identify an optimal level of exercise that results in maximum benefit with minimum risk and to develop evidence-based guidelines for exercise for the SCD population.

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Abbreviations

The following abbreviations are used in this manuscript:

SCD	Sickle cell disease
HbS	Sickle haemoglobin
VCAM-1	Vascular cell adhesion molecule-1
ICAM-1	Intracellular adhesion molecule-1
ROS	Reactive oxygen species
NO	Nitric oxide
RBC	Red blood cell
ACS	Acute chest syndrome
TLR4	Toll-like receptor 4
HbF	Fetal haemoglobin
Exa-cel	Exagamglogene autotemcel
VO2	Oxygen consumption
CPET	Cardiopulmonary exercise testing
CF-PWV	Carotid-femoral pulse wave velocity
CR-PWV	Carotid-radial pulse wave velocity
NOS	Nitric oxide synthase
eNOS	Endothelial nitric oxide synthase
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
PM	Particulate matter

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