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Review Article

Hemolysis and Vaso-Occlusive Crisis in Sickle Cell Disease: A Review

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ABSTRACT

Sickle Cell Disease (SCD) is an inherited condition characterised by haemolysis and Vaso-occlusive crisis (VOC), resulting in considerable morbidity and organ impairment. These crises lead to consequences like stroke, splenic sequestration, and acute chest syndrome, significantly affecting patients quality of life. This review combines information on hemolysis and Vaso-occlusive crises in sickle cell disease, highlighting their aetiology, clinical implications, and prospective treatment approaches to alleviate disease severity.

A systematic review was performed using PRISMA principles. Relevant publications from PubMed, Google Scholar, Web of Science, Scopus, and ScienceDirect were examined, focusing on research published between 2000 and 2024. A total of 68 research articles were included. Haemolysis in sickle cell disease leads to oxidative stress, endothelial dysfunction, and an increased risk of thrombosis. Volatile organic compounds (VOCs) exacerbate these effects, resulting in persistent discomfort, multi-organ impairment, and an increased healthcare burden. Although hydroxyurea remains a fundamental treatment, novel therapies, including voxelotor, crizanlizumab, and gene therapy, exhibit potential. Moreover, antioxidant supplementation, encompassing vitamins D, A, E, and C, has shown promise in mitigating oxidative damage, but clinical results are variable.

Hemolysis and Vaso-occlusive crises are pivotal to the pathophysiology of sickle cell disease, substantially exacerbating consequences and patient distress. Progress in pharmacological and supportive therapy provides optimism for enhanced management. Further study is necessary to determine long-term effectiveness and accessibility.

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INTRODUCTION

Sickle Cell Disease (SCD) is a hereditary disorder characterised by an autosomal recessive inheritance pattern, which leads to alterations in the structure and function of the Haemoglobin (Hb) molecule. This modification converts red blood cells into a sickle or crescent morphology. Sickle cell disease is a highly prevalent genetic disorder with an autosomal recessive inheritance pattern observed globally (Figure 1).[1, 2] Vaso-occlusive crises are pivotal in the pathophysiological process characterising sickle cell disease.

Sickle cell disease (SCD) is a heterogeneous condition characterised by diverse clinical severity, predominantly shaped by genetic differences. Sickle Cell Anaemia (HbSS), the most severe kind, arises from homozygosity for the sickle haemoglobin (HbS) gene and is characterised by recurrent Vaso-occlusive crises (VOC), chronic haemolysis, and an elevated risk of stroke and organ damage.[3] Haemoglobin Sickle C Disease (HbSC), resulting from the co-inheritance of the HbS and Haemoglobin C (HbC) genes, often manifests with less severe anaemia but a heightened risk of consequences, including retinopathy, avascular necrosis, and thrombosis.[4]

HbS-β-thalassemia results from the conjunction of HbS with a β-thalassemia mutation, exhibiting a severity spectrum from moderate (β^+-thalassemia, which maintains partial normal haemoglobin synthesis) to severe (β^0-thalassemia, which resembles HbSS owing to the complete absence of normal haemoglobin)[5] Genotype-based variations affect clinical symptoms and therapeutic responses to hydroxyurea, transfusions, and novel treatments. Comprehending the genetic and phenotypic variation in sickle cell disease is essential for formulating personalised therapy strategies (Table 1).[6]

The relationship between anaemia and crises exerts a significant impact on the manifestation of bone pain.[7-9] The rising incidence of sickle cell disease is generating growing apprehension within the realm of global healthcare. Based on projections, it is anticipated that around 400,000 infants will be diagnosed with sickle cell anaemia by the year 2050.[10-12] The present pathological state is distinguished by the presence of homozygosity in

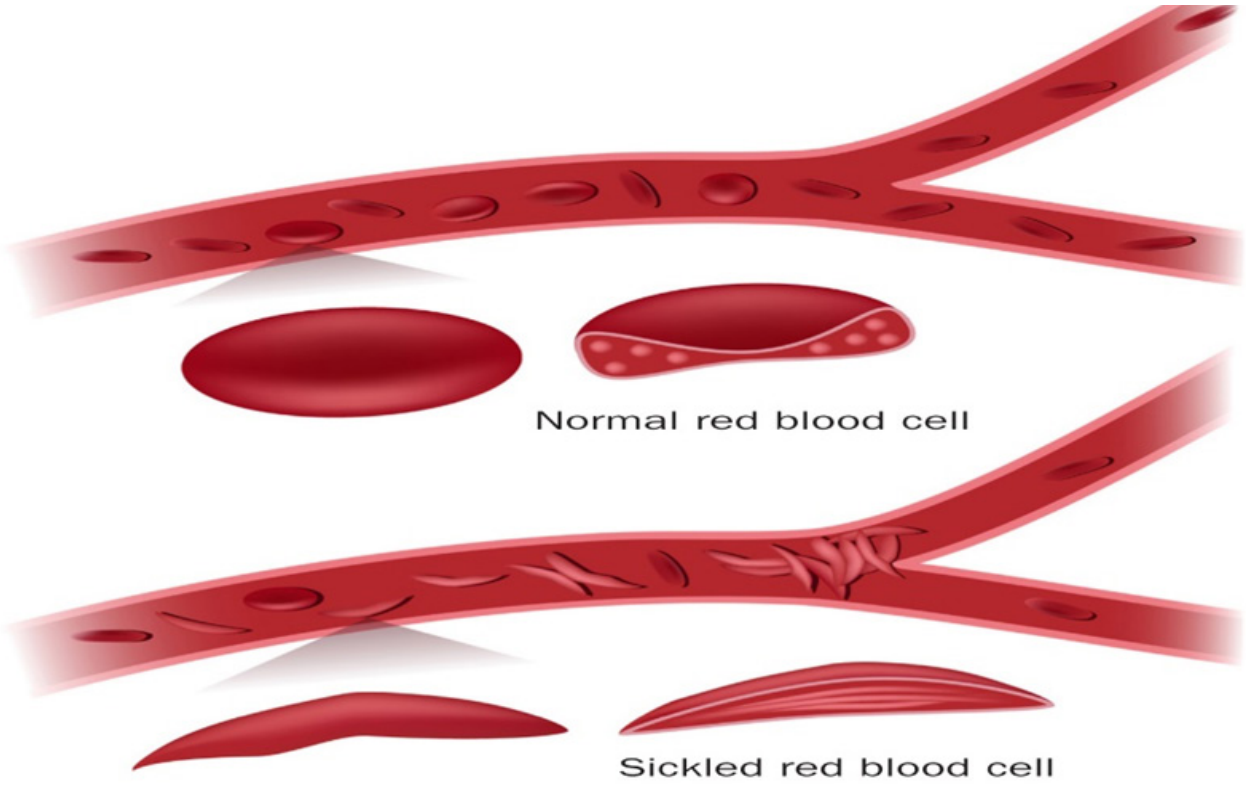

Figure-1. The inherent circular and flexible characteristics of typical red blood cells enable them to navigate the vasculature seamlessly. Sickle cell disease is characterized by abnormal haemoglobin, which results in the deformation of erythrocytes into a sickle or crescent shape, causing them to lose their flexibility. Cells exhibiting anomalous characteristics tend to impede the flow of blood through narrower blood vessels, leading to reduced oxygen supply to tissues, a condition known as tissue hypoxia, which subsequently triggers episodes of distressing pain. Alila Medical Media has produced the visual representation presented in the preceding content.[18]

Table 1. Major Sickle Cell Disease (SCD) Genotypes and Associated Clinical Features.

Genotype	Genetic Basis	Severity	Complications	References
HbSS (SCA)	Homozygous for HbS	Most severe	VOC, chronic hemolysis, stroke, organ damage	[19, 20]
HbSC	HbS + Hemoglobin C	Moderate	Less severe anemia, higher risk of retinopathy, and thrombosis	[21-23]
HbS-β^0-thalassemia	HbS + β^0-thalassemia mutation	Severe	Similar to HbSS	[24, 25]
HbS-β^+-thalassemia	HbS + β^+-thalassemia (partial HbA)	Milder	Moderate symptoms	[26, 27]

the Sickle Haemoglobin S (HbS) gene, resulting from a missense mutation (Glu6Val, rs334) in the -globin gene (HBB). Sickle cell disease is a highly prevalent medical condition that impacts a substantial population globally, exhibiting a higher prevalence among persons of African, South or Central American, Caribbean, Mediterranean, Indian, or Saudi Arabian ancestry. With hemolytic and Vaso-occlusive effects, SCD exhibits a range of thrombotic manifestations, including the occurrence of ischemic stroke.[13, 14] Furthermore, several recent research studies suggest that individuals diagnosed with SCD may exhibit increased susceptibility to Venous Thromboembolism (VTE).[15-17]

Sickle cell disease encompasses a diverse range of potential adverse outcomes, including, but not limited to, hemolytic stress, renal and hepatic insufficiency, and hemolytic and Vaso-occlusive effects. This study examines hemolysis and Vaso-occlusive crises, their significant impact on patients, and the mitigation of these occurrences in affected individuals.

METHODS

Database Selection

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A thorough search was performed utilising PubMed, Google Scholar, Web of Science, Scopus, and ScienceDirect.

Search Strategy

The further search phrases employed were sickle cell disease, haemolysis, Vaso-occlusive crisis, stroke, antioxidants, hydroxyurea, voxelotor, and gene therapy.

Inclusion criteria

The inclusion criteria were papers published between 2000 and 2024, publications addressing hemolysis, Vaso-occlusive crises, oxidative stress, novel treatment strategies in sickle cell disease, and clinical trials or meta-analyses.

Exclusion criteria

The exclusion criteria included studies not conducted in English, animal research, case reports, and conference papers.

Hemolysis

Although the evidence is not as definitive and relies on indirect measures, there is confirmation of a correlation between hemolysis and stroke. Numerous scholarly inquirie.[13] Prior research has established a link between reduced levels of haemoglobin and the incidence of cerebrovascular accidents in individuals with sickle cell disease. Prior research.[13,28,29] has indicated that individuals who have been diagnosed with sickle cell anaemia and thalassemia exhibit a reduced likelihood of experiencing a stroke. Based on the existing empirical evidence, it can be inferred that the implementation of chronic transfusion therapy in young patients diagnosed with sickle cell disease and presenting elevated Transcranial Doppler (TCD) velocities is linked to a simultaneous reduction in hemolysis, plasma haemoglobin concentration, and the likelihood of suffering a stroke. The abovementioned discovery supports the proposition presented in.[30] Concerning the association between hemolysis and the likelihood of experiencing a stroke. Sources.[31, 32] The generation of Reactive Oxygen Species (ROS) in erythrocytes can be attributed to the inherent instability of HbS and an augmented autooxidation mechanism. Furthermore, hemolysis leads to the release of heme, haemoglobin, and iron into the plasma, increasing extracellular ROS concentrations. The acceleration of the Fenton reaction, which leads to the degradation of proteins and polyunsaturated lipids, facilitates a specific process by the presence of iron and heme within the plasma. The one-mentioned event destabilises

erythrocyte membranes, which subsequently causes hemolysis.[33, 34]

Hemolysis is widely recognized as the primary pathophysiological manifestation of SCD, referring to the ongoing breakdown of red blood cells. Prior studies have demonstrated that the repetitive manifestation of this phenomenon results in a decline in antioxidant defences, thereby initiating the onset of oxidative stress.[35-37]

Substantial evidence for the documented roles of vitamins A and E in preventing lipid peroxidation and the disruption of the oxidative process in membranes and lipoproteins.[38, 39] It has been observed that Vitamin D can augment the activation of specific genes, specifically Nrf2 and Klotho, thereby increasing the synthesis of antioxidant enzymes and maintaining redox homeostasis. As a result, this can lead to the manifestation of an antioxidant effect.[40] Multiple studies have provided evidence to support the notion that Vitamin E exhibits the capacity to replenish Vitamin C levels, consequently augmenting the antioxidant characteristics of Vitamin C. Moreover, it has been observed that Vitamin D plays a role in facilitating the synthesis of the tripeptide Glu-Cys-Gly. This tripeptide serves as the primary redox agent and is crucial for maintaining cellular homeostasis and antioxidant mechanisms.[41-43]

Combined with vitamins, minerals such as zinc and selenium demonstrate antioxidative properties. The inhibitory effect of zinc on the NADPH oxidase enzyme has been documented, alongside its ability to confer stability to sulfhydryl proteins. Moreover, zinc competes with other metals capable of undergoing redox reactions, such as copper and iron, to facilitate the Fenton reaction, generating free radicals.[44,45] Zinc serves as a cofactor for the enzymatic activity of Superoxide Dismutase (SOD). Vitamin D Deficiency (VDD) among individuals of Kurdish origin in Iraq who experienced SCD. In particular, a notable proportion of the observed cases, amounting to 78%, displayed a significant insufficiency in vitamin D.[46, 47]

A potential correlation exists between the observed outcome and an increased susceptibility to erythrocyte hemolysis. Individuals who have been diagnosed with Sickle Cell Anaemia (SCA) and sickle cell trait-thalassemia exhibit notably decreased concentrations of total cholesterol, Low-density Lipoprotein (LDL) cholesterol, and High-density Lipoprotein (HDL) cholesterol when exposed to hemolytic stress (Figure 2).[46, 48]

Vaso-Occlusive Crisis

Sickle cell disease is primarily characterised by Vaso-occlusive crisis, also known as acute painful crisis, which represents the primary morbidity associated with this condition. The presence of fever is commonly documented, even in cases of seemingly straightforward painful episodes. This demonstrates that

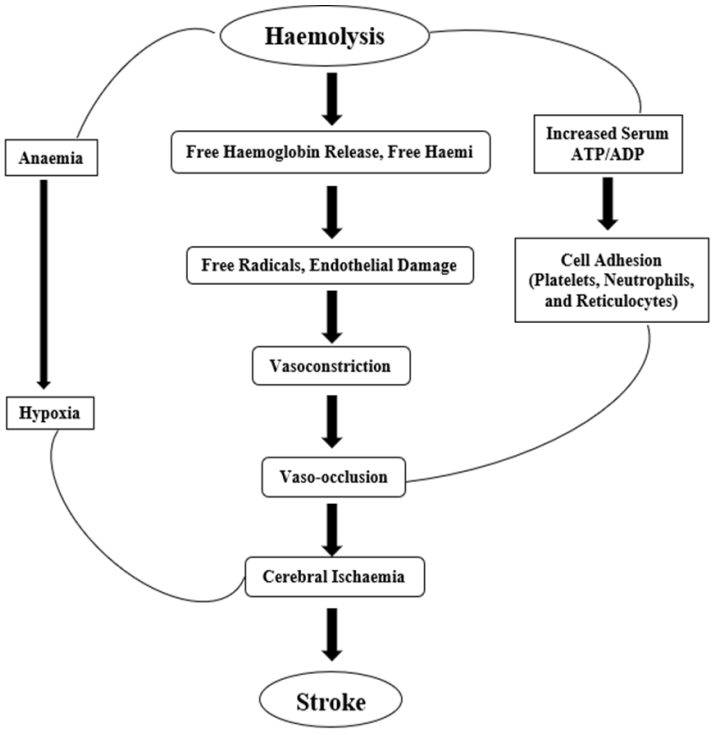

Figure 2. Pathophysiology of Stroke in Sickle Cell Disease (SCD) Hemolysis in sickle cell disease results in anemia, the liberation of free hemoglobin, and elevated ATP/ADP levels. These result in Vaso-occlusion, cerebral ischemia, and ultimately, a stroke.

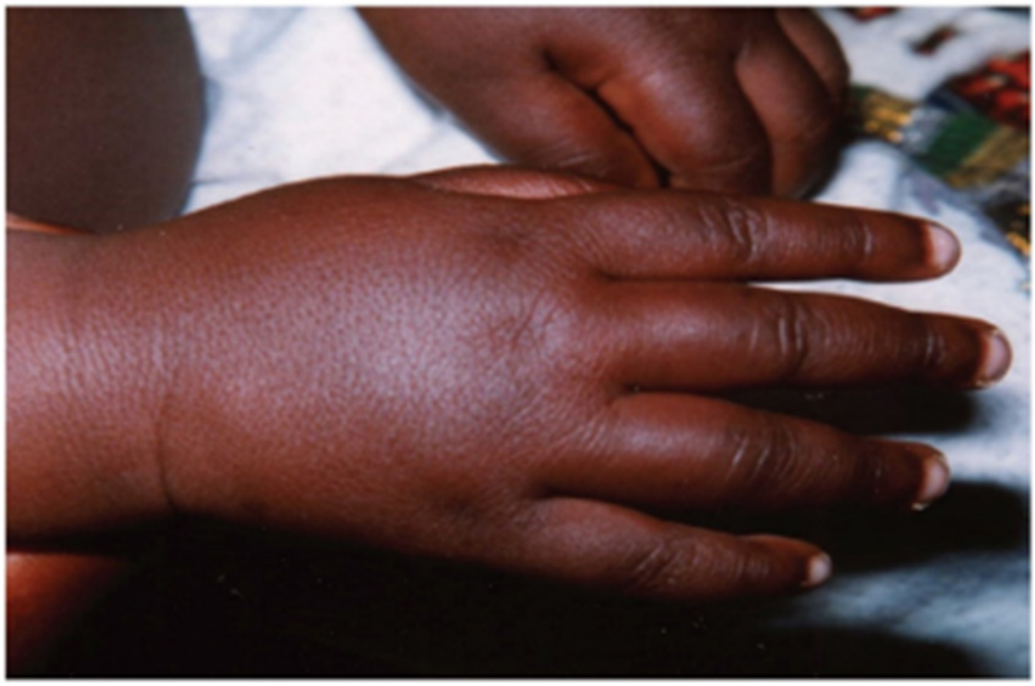

Figure 3. The provided image showcases the hand of a young child exhibiting dactylitis, a distressing medical condition characterised by inflammation and swelling of the digits, specifically the fingers or toes. Tom D. Thacher, MD, generously provided the photograph .[53]

fever can manifest as an isolated occurrence and does not necessarily indicate the presence of a pathological condition.[49, 50] The primary focus of clinical management of Vaso-occlusive Episodes (VOEs) is to assess pain intensity and administer appropriate analgesic medications expeditiously. Dactylitis, a condition characterised by discomfort and swelling in the hands and feet of the individual experiencing it, is commonly observed in infants and toddlers and is believed to result from infarctions. This particular condition has the potential to act as the primary indication of complications linked to SCD (Figure 3).[51, 52]

Sickle Cell Disease is a pathological condition that exhibits four distinct pain syndromes: hemolytic anaemia and its associated consequences, potential organ dysfunction involving infectious processes, and related ailments. The presence of four different components characterises the tetrad and can occur spontaneously or as a result of the other three elements, with pain being the primary clinical manifestation.[54-56]

Pharmacology remains the primary approach for addressing the current situation. Contemporary pain management approaches have advanced to incorporate the physiological dimensions of pain, as well as the psychological, social, and behavioural factors intricately linked to each instance.[57] Implementing a comprehensive pain management strategy is crucial in enhancing the overall well-being of individuals.[58] The findings from studies on pain-related issues suggest that incorporating cognitive behavioural therapy as an adjunctive strategy to complement other pain management interventions may offer benefits for individuals who have been diagnosed with sickle cell disease. The phenomenon above can be attributed to its capacity to alleviate psychological distress and enhance an individual's sense of competence and adaptability.[59]

The Vaso-occlusive crisis encountered by patients has the potential to affect six key domains, namely physical, psychological, social, role-related, overall life satisfaction, and perceived health status.[60] The available empirical evidence indicates that various psychological, societal, and spiritual factors can influence pain perception. In adherence to current guidelines, it is crucial to promptly provide personalised analgesic treatment based on the self-reported pain levels of individuals experiencing Vaso-occlusive crises.[61, 62] Quantitative Sensory Testing (QST) has been employed to determine that individuals aged seven years and older who are affected by SCD exhibit neuropathic pain. This is notable considering that Vaso-occlusive episodes typically result in nociceptive pain.[63, 64]

The available empirical evidence indicates the

presence of a positive correlation between age and the incidence of chronic pain in individuals diagnosed with sickle cell disease.[65] This phenomenon has been linked to the dysfunction of bodily organs, chronic inflammation, and the manifestation of opioid-induced hyperalgesia.[66] Consequently, there have been suggestions to include various supplemental pharmacological substances, for instance, the administration of ketamine at a low dosage level into the course of treatment. In clinical environments, it functions as a regulator of opioid tolerance and opioid-induced excessive pain despite the continued reliance on opioids as the primary method of pain relief. Despite the growing interest in employing this therapeutic approach, there appears to be a lack of available data on its effectiveness in managing pain related to Sickle Cell Disease, as indicated by various sources.[67-69]

Sickle cell disease is distinguished by the presence of Vaso-occlusive crisis (VOC), which can serve as an initial indication of several potentially life-threatening complications, including Acute Chest Syndrome (ACS), stroke, splenic sequestration, and multisystem organ failure.[70] Research findings have suggested that certain instances of Vaso-occlusive Crisis (VOC), a distressing medical condition, may be effectively addressed in a home setting, obviating the necessity for immediate medical intervention or hospital admittance.[71, 72] The mitigation of Volatile Organic Compounds (VOCs) holds significant significance for medical professionals, as these compounds adversely influence the Quality of Life (QOL) experienced by individuals afflicted with SCD. Sickle cell disease imposes a substantial economic burden on affected individuals, negatively impacting their overall health and well-being.[73]

Based on estimations, it was found that minors below the age of 18 who received a diagnosis of SCD accumulated an average yearly expenditure of US$14,772 for employer-provided insurance and US$11,702 for Medicaid healthcare in the year 2005.[74] The insufficient accessibility of preventive and comprehensive healthcare services is a contributing factor to the increasing financial burden associated with medical care for adult patients afflicted with SCD.[75] The circumstances above can be attributed to insufficient insurance coverage and a shortage of healthcare professionals. Consequently, a significant portion of the populace is compelled to seek medical care promptly, leading to an escalation in healthcare expenditures.[76]

Based on a research analysis examining healthcare expenditures from 2001 to 2005, it was determined that the mean monthly healthcare expenditure for individuals within the 50- to 64-year age range was $262. The quantity above exceeded the comparable expenses incurred by individuals aged 0 to 9 by a factor of three.[77] The intricate management of SCD substantially contributes to the disease's intricacy and economic burden. The prioritisation of preventive measures aimed at reducing sudden cardiac death (SCD) during the early stages of life holds great importance.[78]

Preventive measures encompass neonatal screening, the administration of anti-infective injections, and prophylactic antibiotic therapy that is initiated shortly after birth and maintained until the completion of the initial round of vaccinations that specifically target encapsulated microorganisms.[79] Furthermore, a yearly assessment employing transcranial Doppler ultrasound is conducted to ascertain the need for prophylactic transfusion therapy in the prevention of initial strokes and to monitor the probability of stroke incidence for the prediction of neurological complications.[80] The treatment of SCD has witnessed notable progress with the incorporation of various therapeutic modalities, including bone marrow transplant, L-glutamine, voxelotor, and crizanlizumab-tmca, alongside established maintenance medications such as blood transfusions and hydroxyurea. Previous research has shown the effectiveness of Hydroxyurea (HU) in reducing the occurrence of VOC and ACS while also reducing the necessity for blood transfusions and overall utilisation of Healthcare Resources (HCRU).[81] However, the full potential of HU has yet to be fully realised. The efficient management of SCD is hindered by the significant obstacle posed by the increased utilisation of healthcare resources (HCRU) associated with this condition. The utilisation of HCRU is significantly impacted by expensive hospitalisations and emergency room visits, necessitated by heightened service levels and resource requirements.[81, 82]

An abrupt and severe onset characterises the VOC, necessitating prompt interventions such as urgent medical attention and hospital admission to mitigate the potential for serious consequences.[52, 80]. The effective management of VOCs has emerged as a pivotal consideration in the formulation of treatment approaches for Acute Kidney Injury (AKI) associated with sepsis, owing to its significant influence on the utilisation of healthcare resources and related expenses, as well as its correlation with adverse health consequences such as morbidity and mortality.[83]

Stroke

Stroke is a significant and serious consequence of sickle cell disease (SCD), impacting individuals throughout their lives. Retrospective cohort research at the French Adult Sickle-Cell Disease Referral Centre examined 69 stroke cases from a total of 2,875 persons with SCD between 1970 and 2008. The research recorded 104 strokes, including 80 ischemic incidents, 22 hemorrhagic incidents, and 2 cerebral sinus thromboses. Hemorrhagic strokes primarily affected adults and were linked to an increased mortality risk relative to ischemic strokes.[84] The Stroke Prevention Trial in Sickle Cell Anaemia (STOP) was a pivotal, multicenter trial that assessed the efficacy of frequent blood transfusions in reducing the occurrence of first strokes in children with Sickle Cell Disease (SCD). The experiment indicated that sustaining sickle haemoglobin levels at or below 30% with periodic transfusions markedly reduced the incidence of first stroke by a minimum of 70% in comparison to usual treatment.[85]

Notwithstanding progress in preventative measures, current data reveal that the burden of cerebrovascular illness in SCD persists significantly. Research employing statewide data from California indicated that among 7,636 individuals with SCD, the cumulative incidence of the first ischemic stroke was 2.1% by age 20 and 13.5% by age 60.[86] Moreover, studies have indicated that the prevalence of hemorrhagic stroke among SCD patients escalates with advancing age. Structural vascular anomalies, including moyamoya arteriopathy and aneurysms, frequently contribute to hemorrhagic incidents, indicating that screening for these disorders may be advisable.[87]

Antioxidants

Oxidative stress significantly contributes to the pathogenesis of SCD, resulting in hemolysis and Vaso-occlusive crises. Numerous research studies have investigated the potential benefits of antioxidant supplementation in mitigating these symptoms. A Cochrane analysis evaluated the effectiveness of various antioxidants, including vitamin C, in combination with vitamin E, zinc, N-acetylcysteine (NAC), L-arginine, and omega-3 fatty acids. The review indicated that L-arginine could alleviate pain intensity and that zinc could elevate haemoglobin levels; however, the data were inconsistent, and the overall advantages of antioxidants in SCD remain ambiguous.[88] Further research found that omega-3 fatty acids, vitamin A, and zinc enhanced haemolysis parameters, including haemoglobin and hematocrit levels. However, high doses of vitamin C and E supplementation exacerbated haemolysis, as indicated by elevated reticulocyte and lactate dehydrogenase levels.[89]. Furthermore, studies indicate that nutraceuticals abundant in antioxidants, such as alkaloids, polyphenols, vitamins, and minerals, may be prospective therapeutic agents for SCD by mitigating oxidative stress and Vaso-occlusive crises (Table 2).[90, 91]

Therapeutic Interventions

Hydroxyurea

Hydroxyurea has been thoroughly investigated as a treatment for sickle cell disease (SCD), showing considerable advantages across diverse patient groups. A pivotal randomised controlled experiment in 1995 shown that hydroxyurea treatment significantly decreases the incidence of painful crises in people with sickle cell disease, resulting in fewer hospitalisations and transfusion needs.[102] Subsequent studies have validated these findings, emphasising hydroxyurea's effectiveness in reducing Vaso-occlusive events and acute chest syndrome in adults and children.[103, 104]. Hydroxyurea increases foetal haemoglobin (HbF) levels, preventing sickle haemoglobin's polymerisation, thereby diminishing haemolysis and Vaso-occlusion.[105]

Table 2. Antioxidant Agents Studied in Sickle Cell Disease: Clinical Effects and Limitations.

Antioxidant	Benefit	Clinical Evidence/Limitations	References
Vitamin A	Prevent lipid peroxidation	Some positive, inconsistent outcomes	[92]
Vitamin C	Antioxidant effect	High doses increase hemolysis markers	[93, 94]
Vitamin D	Supports enzyme activation/redox	High prevalence of deficiency among SCD patients	[95, 96]
Vitamin E	Membrane/lipoprotein protection	Can enhance vitamin C activity, but high doses may be harmful	[97]
Zinc	Enhances Hb; SOD cofactor	Generally beneficial, some support for pain reduction1	[98]
Omega-3 Fatty Acids	Improved hemolysis parameters	Positive findings in some studies	[99-101]

Moreover, hydroxyurea has demonstrated efficacy in reducing leukocyte and platelet counts, diminishing the expression of endothelial adhesion molecules, and elevating nitric oxide levels, all of which enhance vascular function and mitigate disease consequences.[106] Long-term trials have shown the safety and sustained effectiveness of hydroxyurea, indicating a decrease in mortality among treated individuals (Table 2).[107]

Voxelotor

Voxelotor, branded as Oxbryta, is a crucial therapeutic drug for managing sickle cell disease (SCD) by inhibiting haemoglobin S polymerisation, which reduces haemolysis and elevates haemoglobin levels. The phase 3 HOPE study revealed that voxelotor dramatically increased haemoglobin levels and reduced haemolysis indicators in individuals with sickle cell disease, suggesting its potential as a disease-modifying treatment.[108] Subsequent longitudinal follow-up investigations corroborated these findings, demonstrating persistent enhancements in haemoglobin levels and hemolytic indicators over prolonged durations.[109] Pediatric trials have demonstrated voxelotor's effectiveness, revealing substantial haemoglobin increases in children aged 4 to 11 years (Table 2).[110]

Gene Therapy

Gene therapy has emerged as a viable therapeutic strategy for sickle cell disease (SCD), addressing the genetic basis of the condition. Conventional therapies have predominantly focused on symptom management, although recent innovations offer potential solutions. A significant technique involves procuring autologous hematopoietic stem cells (HSCs) from patients who have undergone ex vivo genetic modification to reduce the propensity for sickling and then reinfusing them. This method has demonstrated considerable therapeutic advancements in many trials, employing lentiviral vector-mediated gene addition to impede haemoglobin aggregation.[111]

In December 2023, the U.S. Food and Drug Administration authorised lovotibeglogene autotemcel (Lyfgenia) for individuals aged twelve and older with sickle cell disease and a history of Vaso-occlusive episodes. This therapy involves the extraction of the patient's hematopoietic stem cells, genetically modifying them to produce a non-sickling variant of haemoglobin, and subsequently reinfusing them after myeloablative conditioning. Clinical trials indicated that 88% of individuals attained full remission of Vaso-occlusive events within six to eighteen months following therapy.[112] Another novel method utilizes CRISPR/Cas9 gene-editing technology to restart fetal hemoglobin synthesis, thereby offsetting the impaired production of adult hemoglobin. This approach has shown encouraging outcomes in the first clinical studies, with patients exhibiting substantial decreases in illness symptoms (Table 3).[113]

Table 3. Comparison of Main Therapeutic Options for Sickle Cell Disease.

Therapy	Mechanism of Action	Efficacy	Limitations	References
Hydroxyurea	Increases HbF, reduces sickling/hemolysis	Reduces VOC, ACS, and improves survival	Adherence, genotype dependence	[114, 115]
Voxelotor	Inhibits HbS polymerization	Increases Hb, lowers hemolysis	New, long-term safety data are limited	[116]
Gene Therapy	Genetic correction of HbS	High remission rates in trials	Cost, accessibility, and unknown long-term effects	[117, 118]

DISCUSSION

This review emphasises the pivotal role of haemolysis and Vaso-occlusive crises in sickle cell disease (SCD), connecting them to stroke, oxidative stress, and inflammation. Current research indicates that hemolysis-induced liberation of free haemoglobin elevates reactive oxygen species (ROS), exacerbating endothelial dysfunction and vascular occlusion.[119] The evidence linking low haemoglobin levels to stroke risk in sickle cell disease is substantial; however, several studies indicate that genetic variables, such as co-inheritance of α-thalassemia, may reduce this risk.[120] Although substantial data support hydroxyurea's efficacy in decreasing VOCs and enhancing foetal haemoglobin levels, its success is contingent upon patient genotype, and adherence continues to pose a barrier.[103] Recently sanctioned therapies, like voxelotor (which mitigates haemolysis) and crizanlizumab (which addresses inflammation), have potential; nonetheless, long-term safety data remain insufficient.[120] Emerging gene treatments provide promising therapeutic solutions, yet their exorbitant cost and accessibility challenges persist as obstacles.[121]

The efficacy of antioxidant treatment in sickle cell disease remains a topic of contention. Although vitamins A, C, D, and E are posited to mitigate oxidative stress, clinical investigations have yielded inconsistent outcomes. Elevated dosages of certain antioxidants may induce oxidative damage, raising concerns about their regular use.[122] This analysis highlights the emotional and economic impact of SCD, a phenomenon that is often overlooked in clinical studies. Numerous patients contend with chronic pain, depression, and opioid dependence, highlighting the necessity for multidisciplinary pain treatment strategies, including cognitive-behavioural therapy (CBT) and alternative analgesics such as low-dose ketamine.[123] Future research should focus on (1) individualised treatment approaches informed by genotype, (2) longitudinal safety data about novel SCD medicines, (3) enhancing antioxidant therapy, and (4) mitigating gaps in healthcare access. Integrating genetic, pharmacological, and psychological strategies will enhance outcomes for SCD patients globally.

CONCLUSIONS

Sickle Cell Disease is a considerable global health concern, with haemolysis and Vaso-occlusive crises substantially exacerbating its course. The pathophysiological pathways encompass inflammation, oxidative stress, and endothelial dysfunction, leading to severe outcomes such as stroke, acute chest syndrome, and organ failure. While hydroxyurea has substantially reduced disease severity, novel medicines like voxelotor, crizanlizumab, and gene editing methods provide compelling alternatives. Nevertheless, barriers to accessibility and the lack of long-term safety data persist as ongoing issues. Antioxidant therapy, primarily utilizing vitamins A, C, D, and E, has shown promise in mitigating oxidative stress; however, variable clinical results necessitate further investigation. A customised therapy approach improves therapeutic outcomes by considering genetic factors, including HbS genotypic variations and co-inherited modifiers such as α-thalassemia. Alongside medicinal interventions, the emotional and financial difficulties of SCD must be addressed. Comprehensive treatment modalities, including cognitive-behavioral therapy and multidisciplinary pain management, are essential for improving patients' quality of life. Future research must focus on improving treatment approaches, expanding access to innovative drugs, and addressing the healthcare disparities that consistently affect individuals with SCD worldwide.

Conflict of Interest

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Authors' Contribution

Study Conception: A.M.Q., A.H.H; Study Design: A.M.Q.; A.H.H; Literature Review: A.H.H; Critical Review: A.M.Q; Writer: A.H.H.; A.M.Q..

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