A Review of Pathophysiology, Prevalence, Diagnosis, Therapeutic Approaches, and Nutritional Considerations in Sickle Cell Disease

Rawan Mohammed Hazi Al-Ruwaili [1], Nuha Naif Alshammari [2], Salman Ghazi Al-Faridi [3]

Abstract

Sickle cell disease (SCD) is a chronic genetic disorder caused by mutations in the β-globin gene, resulting in the production of hemoglobin S (HbS). This mutation causes erythrocytes to assume a sickle shape, leading to vaso-occlusive crises, hemolysis, and multi-organ damage. SCD, inherited in an autosomal recessive pattern, manifests in various forms such as sickle cell anemia (HbSS), sickle cell-hemoglobin C (HbSC), and sickle cell-beta thalassemia, with HbSS being the most severe. The disease burden is disproportionately high in Sub-Saharan Africa, where SCD contributes to significant child mortality. Despite advances in treatments such as hydroxyurea, stem cell transplantation, and gene therapy, therapeutic outcomes remain suboptimal. The pathophysiology of SCD is complex, involving factors such as hemolysis, chronic inflammation, and oxidative stress. Emerging therapies, including voxelotor and crizanlizumab, target specific aspects of SCD, such as HbS polymerization and vascular occlusion. The role of fetal hemoglobin (HbF) induction in modulating disease severity has garnered attention, though strategies to enhance HbF production require further development. Additionally, nutritional interventions have been recognized as crucial in managing SCD, as individuals often experience nutritional deficiencies exacerbated by increased energy and protein demands. This review explores the global prevalence, clinical manifestations, and therapeutic approaches to SCD, emphasizing the need for novel treatments and comprehensive public health initiatives to address this pervasive condition. Further research is essential to improve diagnostic methods, treatment modalities, and overall patient outcomes, particularly in resource-limited regions where SCD's impact is most severe.

Keywords: Sickle cell disease, Hemoglobin S, Genetic mutations, Therapeutic strategies, Nutritional interventions

Significance | This review discusses the Sickle cell disease necessitating urgent research into improved therapies, early diagnosis, and comprehensive nutritional support for better patient outcomes.

*Correspondence. Rawan Mohammed Hazi Al-Ruwaili, Clinical Laboratory Sciences Department, Al-Jouf University, King Khalid Road, Sakaka, Kingdom of Saudi Arabia.
E-mail: nooonhnooone@gmail.com

Editor Md Shamsuddin sultan khan, Ph.D., And accepted by the Editorial Board January 09, 2023 (received for review November 09, 2022)

Introduction

Sickle cell disease (SCD) is a chronic, hereditary hemoglobinopathy that continues to be a major global health concern, despite advances in medical research and treatment strategies. It is caused by a genetic mutation in the β-globin gene (HBB), leading to the production of abnormal hemoglobin S (HbS), which polymerizes under deoxygenated conditions, causing erythrocytes to assume a characteristic sickle shape (Elendu et al., 2023). This morphological alteration disrupts normal blood flow, leading to vaso-occlusive crises, chronic hemolysis, and multi-organ complications (Tebbi, 2022; Quinn, 2016). SCD is inherited in an autosomal recessive manner, with sickle cell anemia (SCA) representing the most severe form of the disease, caused by the homozygous presence of the HbS allele (Inusa et al., 2019).

Author Affiliation.
[1] Clinical Laboratory Sciences Department, Al-Jouf University, King Khalid Road, Sakaka, Kingdom of Saudi Arabia.
[2] Department of Applied Human Sciences, Eastern Kentucky University, 521 Lancaster Avenue, 102 Burrier, Richmond, KY 40475, United States.
[3] Ministry of National Guard Health Affairs, Riyadh 11426, Kingdom of Saudi Arabia.

Please Cite This:
Al-Ruwaili, R. M. H., Alshammari, N. N., Al-Faridi, S. G. (2023). "A Review of Pathophysiology, Prevalence, Diagnosis, Therapeutic Approaches, and Nutritional Considerations in Sickle Cell Disease", Journal of Angiotherapy, 7(1),1-12,10144

The hemoglobin molecule comprises two alpha and two beta polypeptide chains, which play a fundamental role in oxygen transport. Mutations in the HBB gene lead to variations such as hemoglobin C (HbC), hemoglobin E (HbE), and hemoglobin S (HbS) (Aldakeel et al., 2020). The substitution of glutamic acid with valine at the sixth position of the β-globin chain in HbS results in reduced hemoglobin solubility and polymerization under hypoxic conditions (Venugopal et al., 2018). This mutation underlies the pathophysiology of SCD, contributing to erythrocyte rigidity, adhesion, and subsequent vascular obstruction (Mangla et al., 2023). The clinical manifestations of SCD include anemia, recurrent pain crises, organ damage, and increased susceptibility to infections (Egesa et al., 2022). Additionally, hemolysis and chronic inflammation play significant roles in disease progression, exacerbating endothelial dysfunction and promoting oxidative stress (Nader et al., 2020; Liu et al., 2023).

The heterogeneity of SCD is influenced by various genetic and environmental factors. Different genotypes of the disease include HbSS (sickle cell anemia), HbSC (a less severe variant), HbSβ-thalassemia, and other rare hemoglobinopathies (Uçucu et al., 2022). The severity of symptoms varies among individuals, with some experiencing mild forms while others suffer from life-threatening complications such as stroke, acute chest syndrome, and pulmonary hypertension (Habara & Steinberg, 2016; Njoku et al., 2021). The role of fetal hemoglobin (HbF) in modulating disease severity has been extensively studied, as elevated HbF levels reduce HbS polymerization and improve clinical outcomes (Kargutkar et al., 2023). However, therapeutic approaches to induce HbF expression remain suboptimal, necessitating further research to enhance treatment efficacy.

Pain is a hallmark feature of SCD, often presenting as acute vaso-occlusive episodes or chronic debilitating pain (Takaoka et al., 2020). The molecular mechanisms underlying sickle cell pain remain poorly understood but are believed to involve neurogenic inflammation, oxidative stress, and nociceptive sensitization (Sadler et al., 2023). The management of chronic pain in SCD patients is challenging due to the variability in pain perception and the risk of opioid dependence (Osunkwo et al., 2020). Emerging studies are exploring novel therapeutic targets to alleviate pain and improve the quality of life for SCD patients (Matthie et al., 2019).

Despite being one of the most studied genetic disorders, SCD remains a neglected disease in many parts of the world, particularly in sub-Saharan Africa, where the highest disease burden exists (Egesa et al., 2022). Advances in gene therapy and genome editing have opened new avenues for curative treatment, but access to these innovations is limited in resource-constrained settings (Stuart & Nagel, 2004). Continued efforts in research, public health interventions, and global collaboration are essential to improving the prognosis and quality of life for individuals affected by SCD.

2. The Prevalence of Sickle Cell Disorder

Sickle cell disorder (SCD) significantly contributes to multimorbidity and reduced quality of life, while simultaneously placing a considerable strain on healthcare systems in affected regions (Matthie et al., 2019; Osunkwo et al., 2020). The global burden of SCD has been extensively assessed, emphasizing the heightened risk of child mortality associated with sickle cell anemia (SCA) (Thomson et al., 2023). In Sub-Saharan Africa, SCD is responsible for up to 90% of under-five mortality, with nearly 500 children dying daily due to delayed diagnosis and insufficient access to comprehensive treatment—a trend that necessitates urgent intervention (Egesa et al., 2022).

Globally, between 300,000 and 400,000 neonates are born annually with SCA, and tens of thousands present homozygosity for hemoglobin S, the most severe clinical manifestation of the disorder (Grosse et al., 2011; Delgadinho et al., 2022; Ranque et al., 2022; Ali Hazzazi et al., 2020). Although SCD affects populations worldwide, Sub-Saharan Africa bears the highest prevalence, with approximately 1,000 infants born with SCD each day, over half of whom die before the age of five (Arji et al., 2023). Many of these deaths are linked to preventable chronic complications. Various initiatives have been implemented to establish achievable goals aimed at improving both short- and long-term outcomes. These programs focus on addressing the disproportionate attention given to this genetic disorder, particularly in low-income countries (Piel et al., 2023).

While comprehensive epidemiological data for all hematological disorders remain scarce, SCD is estimated to affect over 250 million people globally (Sedrak & Kondamudi, 2023; Piel et al., 2013). Despite the increasing global burden of SCD, which impacts more than 20 million individuals and accounts for approximately 200,000 annual births of the sickle genotype in Sub-Saharan Africa, data on the incidence, mortality, and morbidity of SCA remain inadequate worldwide. However, several systematic reviews have provided global statistical insights (Ansong et al., 2013; Colombatti et al., 2023; Adigwe et al., 2023).

Certain regions, including Egypt, Côte d'Ivoire, Sudan, areas around Lake Chad and Lake Victoria, Tanzania, the Kenyan coast, eastern Madagascar, and Mozambique, exhibit HbS allele frequencies ranging from 7.5% to 12.5% (Piel et al., 2013). Hematological studies in northern Mozambique report an incidence of sickle cell trait (HbAS) and glucose-6-phosphate dehydrogenase (G6PD) deficiency at approximately 4% (Piel et al., 2013; Colombatti et al., 2023).

The sickle cell trait (HbAS) is more prevalent in West Africa, where carriers possess significant immunity against severe *Plasmodium falciparum* malaria. This protective effect persists despite the complex and not fully understood interactions between HbAS,

malaria, and other factors contributing to child mortality (Piel et al., 2013; Ranque et al., 2022; Arji et al., 2023).

3. Diagnosis of Sickle Cell Disease

Sickle cell disease can be prevented through prenatal interventions and detected either in utero or during the neonatal period via screening. Early diagnosis is crucial for initiating treatments that mitigate the risk of severe complications, such as infections and strokes, while effectively managing the disease to reduce morbidity. SCD diagnosis involves comprehensive blood tests, peripheral blood smears, hemoglobin electrophoresis, high-performance liquid chromatography (HPLC), and various genetic assays. The hemoglobin S solubility test and sodium metabisulfite test are commonly used for screening individuals aged six months and older. Screening for pregnant women is recommended before 10 weeks of gestation.

Recent research has explored innovative portable devices for early detection and assessment of SCD and carrier states (Elendu et al., 2023; Tebbi, 2022; Quinn, 2016). Advanced molecular genetic diagnostic tests are also available, providing more precise identification of genetic variations associated with SCD (Aldakeel et al., 2020).

4. Contemporary Therapies for Sickle Cell Disease

A conclusive cure for sickle cell anemia (SCA) remains elusive, despite substantial advancements in understanding and managing the disease. This review aims to elucidate current developments in therapies for SCA and highlight the unmet need for novel therapeutic interventions. It also offers a global overview of prevailing treatment approaches, primarily dominated by blood transfusions.

One of the most promising therapeutic strategies involves the augmentation of fetal hemoglobin (HbF) synthesis, which can mitigate the severity of clinical manifestations in both β-thalassemia and SCA. Elevated HbF levels can significantly reduce disability, morbidity, and mortality associated with these conditions (Kargutkar et al., 2023).

The American Society of Hematology (ASH) has established evidence-based guidelines to aid healthcare professionals in managing pain in SCA patients, encompassing both pediatric and adult populations. However, these guidelines fall short in providing specific directives regarding dietary interventions and supplementary measures (Elendu et al., 2023; Tebbi, 2022).

Sickle Cell Disease (SCD) arises from a genetic mutation that substitutes valine for glutamic acid in the hemoglobin molecule. Although gaps remain in our understanding of glutamine's biological mechanisms and therapeutic implications, the FDA approved L-glutamine (10–30 g/day, oral powder, twice daily) in 2017 for individuals aged five and older to decrease the frequency of pain crises (Inusa et al., 2019).

Historically, hydroxyurea, an oral chemotherapeutic agent and ribonucleotide reductase inhibitor, was the sole FDA-approved disease-modifying treatment for SCA. Despite its proven efficacy, hydroxyurea remains underutilized in clinical settings (Mangla et al., 2023). More recently, a new class of drugs targeting hemoglobin S (HbS) polymerization, such as voxelotor, received FDA approval in 2019 and EMA approval in 2022. These agents are intended for the oral management of hemolytic anemia and vaso-occlusive crises (VOC) in individuals aged 12 and older (Thom et al., 2013).

Voxelotor functions by binding to and stabilizing hemoglobin, thereby inhibiting polymerization and preventing the formation of sickle-shaped red blood cells (Aldakeel et al., 2020). In high-income countries, three primary interventions—blood transfusions, hydroxyurea, and hematopoietic stem cell transplantation—have been pivotal in reducing SCA-related morbidity and mortality (Egesa et al., 2022). Conversely, corticosteroids have shown no efficacy in managing acute SCD episodes (Uçucu et al., 2022).

The polymerization of abnormal hemoglobin S during tissue deoxygenation leads to red blood cell deformation and circulatory obstruction, hallmark features of SCD. Consequently, considerable research efforts have focused on identifying agents capable of modulating non-polymerizing hemoglobin derived from neonates (Liu et al., 2023).

Crizanlizumab, a monoclonal antibody targeting P-selectin, has been approved for both the prevention and treatment of VOC in SCD. This therapy alleviates pain by inhibiting the adhesion of blood cells to the endothelial lining of blood vessels. Monthly administration of crizanlizumab has demonstrated efficacy in reducing the frequency of sickle cell pain crises (Nader et al., 2020; Venugopal et al., 2018).

Another emerging therapeutic avenue involves the activation of the nuclear factor erythroid 2-related factor 2 (NRF2) by sulforaphane, a compound found in cruciferous vegetables like broccoli and Brussels sprouts. NRF2 activation may offer benefits such as reducing liver damage, restoring oxidative balance, and increasing HbF levels in SCD patients (Sadler et al., 2023).

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for severe congenital anemias, including SCD. This procedure involves transplanting healthy stem cells from compatible donors to replace the defective hematopoietic system of the patient. HSCT has been successfully employed in both malignant and non-malignant hematologic conditions (Matthie et al., 2019).

The gut microbiota, comprising approximately 10^13 to 10^14 microbial cells, plays a crucial role in human health, influencing neurological, autoimmune, metabolic, and genetic disorders. In SCD patients, increased gut permeability, altered microbiota

composition, and bacterial translocation suggest a state of dysbiosis that exacerbates systemic inflammation (Osunkwo et al., 2020).

The gut microbiota is intricately involved in energy homeostasis, immune regulation, and various physiological processes. The human genome interacts with the gut microbiota through enzymes and microRNAs, creating a complex interplay between genetic and environmental factors within the gastrointestinal tract (Delgadinho et al., 2022).

This interaction influences inflammatory processes, cell adhesion, and the production of aged neutrophils, which are primary mediators of recurrent VOC. Despite the recognized impact of host genetics on gut microbiome composition, our understanding of the bidirectional relationship between the microbiome and host genes in complex diseases like SCD remains incomplete (Ranque et al., 2022).

Emerging therapeutic strategies targeting gene modulation have shown promise. Techniques such as synergistic gene insertion and gene knockdown in stem cell derivatives have demonstrated proof of concept in preclinical studies. These approaches hold potential for addressing the genetic underpinnings of SCD (Ali Hazzazi et al., 2020).

Chronic pain and osteoporosis are prevalent complications in SCD, yet their etiologies are not fully understood. Recent evidence suggests that the gut microbiome may influence chronic pain management in SCD, as gut barrier dysfunction and microbial translocation contribute to systemic inflammation and pain (Arji et al., 2023).

While significant progress has been made in the management of SCD, substantial gaps remain in our understanding and treatment of the disease. Continued research into novel therapies, including gene editing, microbiome modulation, and pharmacological advancements, is essential to improve outcomes and quality of life for individuals living with SCD.

5. Nutritional Considerations in Sickle Cell Disease

Nutritional abnormalities are increasingly recognized as significant contributors to the severity and progression of sickle cell disease (SCD). This recognition has spurred interest in advocating for nutritional interventions, especially in light of the limited availability of effective treatments for SCD (Elendu et al., 2023). Individuals with sickle cell anemia (SCA) often require higher energy and protein intake compared to healthy individuals, making them susceptible to undernutrition if their dietary needs are not adequately met (Tebbi, 2022). Despite this, there is limited research on dietary therapies that could serve as adjunctive aids in SCD treatment.

Poor dietary habits are a well-known risk factor that can adversely affect clinical outcomes, overall well-being, essential physiological functions, and patient autonomy. There remains a gap in understanding how nutrition can be integrated into comprehensive medical care for SCD. Increasing awareness of the critical role diet plays in managing and treating SCD is imperative (Quinn, 2016). Nutritional recommendations, particularly for children with SCD, should be prioritized to mitigate disease complications and improve quality of life.

Key factors exacerbating SCD include chronic inflammation and oxidative stress, highlighting the necessity of formulating specific dietary reference intakes for individuals with SCA. Nutritional therapy should be integrated as an adjunct to routine medical procedures (Ershler et al., 2023). Given the absence of a simple and cost-effective treatment, recent efforts have focused on dietary interventions to alleviate health complications and enhance the quality of life for people with SCD. However, existing guidelines for daily nutrient intake and dietary standards for the general population are often insufficient for addressing the unique needs of SCD patients (Inusa et al., 2019).

Recent studies underscore the significance of malnutrition as a complication of SCD and the potential benefits of consistent micronutrient supplementation (Kargutkar et al., 2023; Thom et al., 2013). Symptoms of SCD typically manifest around five months of age and vary among individuals, marked by episodes of pain, fatigue, recurrent infections, organ damage, and early mortality. These symptoms can lead to growth retardation in children, necessitating increased intake of nutrients such as protein and calories (Aldakeel et al., 2020).

Chronic ischemia-reoxygenation injury, often resulting from vaso-occlusive crises (VOC), can lead to intestinal permeability in SCD patients. This impacts the gut microbiota, adherence to the epithelial lining, and the degree of bacterial translocation, which in turn affects nutrient absorption, metabolic balance, hormonal regulation, microbial composition, and immune function (Egesa et al., 2022). Identifying dietary deficiencies common in SCD and developing innovative nutritional strategies are crucial for reducing morbidity and enhancing life quality (Uçucu et al., 2022).

SCD has been associated with vitamin D deficiency and reduced appetite. Despite numerous studies, the quality of evidence remains insufficient to inform clinical practice conclusively (Liu et al., 2023). Understanding gene-nutrient interactions to determine specific responses across different ethnic and environmental contexts remains challenging (Nader et al., 2020). Nutritional deficiencies are prevalent in SCD and may correlate with increased pain episodes (Thom et al., 2013). Addressing these complexities requires a collaborative approach encompassing staple foods, micronutrients, and phytonutrients essential for optimal health and well-being. Emphasis should be placed on improving digestibility, gut health, overall vitality, and mental health (Mangla et al., 2023).

Children with inherited disorders like SCD may experience feeding difficulties and dysphagia due to a complex interplay of anatomical,

physiological, pharmacological, and behavioral factors. These challenges can make eating difficult, passive, or painful, leading to issues such as breathlessness, inability to speak, choking, coughing, fatigue, or vomiting. This may result in children ceasing to eat independently, necessitating parental assistance (Venugopal et al., 2018). Despite the improbability of iron deficiency in SCD patients, due to the homozygous SCA genotype being associated with the most severe disease manifestations, dietary intake has received limited attention, and recommendations for reducing dietary iron remain contentious

The disease process of SCD has profound nutritional and health implications, including increased energy and nutrient demands, dietary deficiencies, and growth abnormalities (Stuart & Nagel, 2004). These findings, however, are based on limited sample sizes, particularly in Sub-Saharan Africa, where SCD is most prevalent. Further research into the potential benefits of nutrition-related interventions for these populations is urgently needed. Over the past decade, fundamental, clinical, and epidemiological research on food, diet, nutrients, and nutrition in individuals with SCD and thalassemia has been identified as a key area for innovation (Habara & Steinberg, 2016).

Evaluating dietary intake in SCD patients has been challenging due to difficulties in assessing food consumption, nutritional inadequacies, and the use of both nutritive and non-nutritive supplements. Additionally, these patients, particularly children under five, are more susceptible to infections from specific bacteria (Du et al., 2018). Poor nutritional data in developing countries has exacerbated the likelihood of adverse outcomes in SCD (Njoku et al., 2021). Encouraging the consumption of minimally processed foods rich in antioxidants should be considered, given their potential benefits in mitigating SCD complications (Takaoka et al., 2020).

Micronutrient deficiencies in SCD patients can increase susceptibility to growth failure, inflammation, opportunistic infections, and acute pain crises (Sadler et al., 2023).

Deficiencies in iron, zinc, copper, folic acid, pyridoxine, and vitamin E have been extensively studied and addressed. While folic acid supplementation may elevate blood folate levels, its impact on SCD outcomes remains unclear. Randomized clinical trials have assessed the efficacy of antioxidant supplements in reducing hemolysis in SCD patients, with mixed results. For instance, vitamins C and E, when administered at safe doses, have been found to exacerbate hemolysis. Conversely, supplementation with omega-3 fatty acids, vitamin A, and zinc has shown improvements in indirect markers of hemolysis (Osunkwo et al., 2020).

Preliminary meta-analyses suggest that supplementation with the semi-essential amino acid L-arginine or its derivatives has beneficial effects in individuals with sickle cell disease (SCD) (Elendu et al., 2023). L-arginine is endogenously synthesized from the metabolism of proline, glutamate/glutamine, and citrulline, a nonproteinogenic amino acid. This synthesis is critical for several physiological functions, including cell division, wound healing, protein synthesis stimulation, immune system enhancement, and hormone secretion (Tebbi, 2022).

In sickle cell anemia (SCA), the increased production of reactive oxygen species (ROS) is a direct consequence of the activation of multiple prooxidant enzymes, which under normal conditions help maintain a balance between oxidant and antioxidant mechanisms, thus preventing oxidative damage. However, the characteristic hemolysis of sickle-shaped red blood cells leads to the release of free hemoglobin, disruptions in mitochondrial respiratory chain function, and the autooxidation of red blood cells, all of which exacerbate oxidative stress (Du et al., 2018).

Excessive free radicals can cause cellular damage, contributing to disease progression and aging, and intensifying oxidative stress in erythrocytes, endothelial cells, polymorphonuclear leukocytes, and thrombocytes. This oxidative stress is closely linked to multiorgan dysfunction, vasculopathy, and cellular anomalies (Quinn, 2016). Although antioxidant therapies have faced various limitations and challenges, certain foods rich in potent antioxidant enzymes may significantly mitigate oxidative-related complications. This has led to the development of dietary interventions aimed at enhancing antioxidant levels in SCA patients (Nader et al., 2020).

Nevertheless, free radicals rapidly interact with proteins, lipids, and nucleic acids within cell membranes, complicating their efficient neutralization by exogenous antioxidants (Njoku et al., 2021). Consequently, accumulating these radicals in living organisms using foreign chemicals has been deemed impractical (Ershler et al., 2023). Reduced levels of polyunsaturated fatty acids (PUFAs) in the phospholipids of cell membranes in children with SCD are not due to dietary deficiencies but rather to altered fatty acid elongation and desaturation processes on the endoplasmic reticulum membrane, which contribute to the manifestation of disease symptoms (Aldakeel et al., 2020).

A potential dietary strategy, when combined with appropriate medical treatments, should focus on moderating the mechanisms of free-radical substitution reactions. This involves maintaining a balance between the production and elimination of free radicals, achievable through a diet rich in nutrient-dense, high-antioxidant foods.

In SCD patients, the antioxidant defense mechanism is significantly impaired due to decreased expression and activity of key antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. These enzymes are essential for breaking down hydrogen peroxide and regulating its intracellular levels (Habara & Steinberg, 2016). In African contexts, integrating conventional and pharmaceutical therapies is crucial, fostering synergy between scientific advancements and traditional

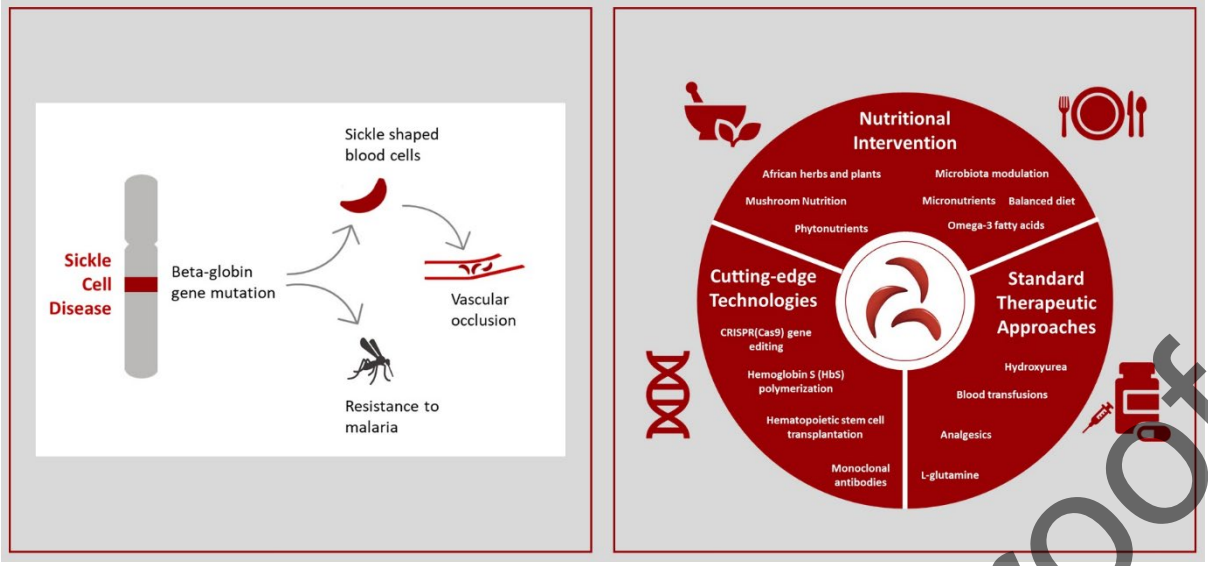

Figure 1. Sickle cell disease.

Figure 2. Certain tropical flora used in SCA inside Sub-Saharan Africa.

knowledge, while addressing the stigma surrounding SCD. Historically, considerable attention has been given to the therapeutic potential of indigenous African plants and herbs, with extensive research into new pharmaceuticals through molecular pharming (Piel et al., 2013).

Research into herbal remedies is gaining traction as a holistic approach to managing SCD, particularly in Africa, where biodiversity is abundant. Traditional healers utilize up to 5,000 native medicinal plants, directly harvested from the wild, serving approximately 80% of the African population. These traditional treatments, supported by empirical evidence of their efficacy over time, are often preferred over pharmaceutical drugs. However, the oral transmission of this knowledge poses a risk of loss among newer generations, who may be reluctant to embrace these traditions (Egesa et al., 2022).

Bioactive compounds in these tropical herbs interact with gut microbiota and available phytonutrients, playing a critical regulatory role in human health (Delgadinho et al., 2022). Numerous systematic reviews have been conducted in Sub-Saharan Africa, where around 80% of global SCA cases are concentrated. These surveys aimed to assess the various challenges and dietary practices of individuals with SCA, identify knowledge gaps, and prioritize future research areas (Piel et al., 2013; Ansong et al., 2013; Colombatti et al., 2023).

Most research on the dietary benefits for African SCD patients has been conducted in Nigeria, with limited studies in other Sub-Saharan countries such as Kenya, Sudan, Tanzania, Malawi, Ghana, Ivory Coast, Cameroon, Mali, and Gabon. This research has explored native therapeutic sources, including seed oils from *Ipomoea involucrata*, *Solenostemon monostachyus*, and *Carica papaya*, as well as commercial extracts from *Cajanus cajan* and *Acacia senegal* seed oil (Piel et al., 2013).

The leaves, root bark, and seeds of *Alchornea cordifolia* (Christmas bush) and *Ceiba pentandra* are both wild-harvested and cultivated for medicinal purposes in the Democratic Republic of Congo. These plants are utilized to create a beverage known as "blood tonic," commonly consumed by individuals suffering from sickle cell anemia (SCA; Elendu et al., 2023). *Moringa oleifera*, prevalent throughout Africa, is rich in phytochemicals with antiurolithiatic properties, and it plays a significant role in the management of sickle cell disease (SCD; Tebbi, 2022). In Sudan, research on *Nigella sativa* (black cumin seed) oil extract—recognized for its calcium antagonist and antioxidant properties beneficial in managing SCA—revealed considerable in vitro anti-sickling activity (Quinn, 2016).

Recent evaluations have assessed traditional herbal treatments employed by physicians across Africa and beyond for treating SCD (Ershler et al., 2023). The urgent demand for safe, effective, and affordable therapeutic agents in Africa underscores the need to enhance SCD care, focusing on medical prevention and managing severe complications, both of which can be improved through dietary interventions (Inusa et al., 2019). Exogenous food-derived microRNAs, acquired through cross-kingdom regulation, may infiltrate the human host via mushrooms, sea algae, and herbal teas, offering novel therapeutic effects by influencing the interactions of microRNAs among food, host, and gut microbiota (Kargutkar et al., 2023; Thom et al., 2013; Aldakeel et al., 2020).

Studies have demonstrated a robust correlation between oxidative stress, inflammatory processes, immune responses, and the pathophysiology of SCD, highlighting the significance of the natural immune system (Egesa et al., 2022; Uçucu et al., 2022). While medicinal plants have a long history of use, data on African mushrooms in healthcare remain limited (Liu et al., 2023; Nader et al., 2020). Edible therapeutic mushrooms, in the form of biomass, extracts, or derivatives, are potential sources of bioactive compounds capable of modulating immunity (Mangla et al., 2023). These compounds exhibit diverse pharmacological properties, including multitarget biological activities, low toxicity, high safety, and cost-effectiveness, making them valuable therapeutic resources (Venugopal et al., 2018).

Fungal biochemical compounds include carbohydrates, carbohydrate-binding proteins (Liu et al., 2023), mono- and polyunsaturated fatty acids, phenolic substances, indole compounds, vitamins, terpenoids, and unique molecules (Elendu et al., 2023; Tebbi, 2022; Quinn, 2016).

Natural products are renowned for their ability to target multiple pathways, offering numerous health benefits. Foods rich in natural antioxidants include berries, avocados, apples, cruciferous vegetables, almonds, olive oil, legumes, tomatoes, and mushrooms (Liu et al., 2023). Mushrooms possess potent anti-inflammatory properties and, though often underappreciated as a therapeutic resource in Western countries, are increasingly recognized for their potential in adjunctive dietary interventions for sickle cell disease.

Consumption of edible mushrooms, whether in their natural form or as supplements (extracts or biomass), has been documented as a powerful means of enhancing wellness, longevity, and quality of life (Mangla et al., 2023). Their mechanism of action is attributed to their unique composition, including the amino acid ergothioneine, β-glucans, specific enzymes, and secondary metabolites. Recent studies have explored the interactions between mushroom bioactive components and gut microbiota, highlighting their effects on metabolism and health conditions (Egesa et al., 2022; Uçucu et al., 2022). Certain mushrooms are rich in superoxide dismutase, glutathione peroxidase, catalase, and proteases, which interact with transcription factors like nuclear factor erythroid 2-related factor 2 to maintain cellular redox homeostasis and reduce oxidative stress. The regulatory effects of active mushroom compounds, such as polyphenols, on ferroptosis have been increasingly recognized

(Kargutkar et al., 2023). Edible mushrooms contain gallic acid, a natural hydroxybenzoic acid that inhibits ferroptosis, which is also present in nuts, red fruits, olive oil, green tea, and vegetables (Mangla et al., 2023). Ferroptocide, a thioredoxin inhibitor, induces ferroptosis, a distinct form of programmed cell death separate from apoptosis, and helps regulate redox balance in sickle red blood cells (Elendu et al., 2023).

Oxidative stress plays a critical role in SCD, driven by an overproduction of reactive oxygen species that exceed the neutralizing capacity of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase. This imbalance activates various inflammatory pathways, impacting redox equilibrium, hemolysis, vasculopathy, and immune response regulation in sickle cell disease (Inusa et al., 2019).

Studies on *Ganoderma lucidum* extracts demonstrated a significant reduction in hemoglobin polymerization, enhancing oxygen binding and preserving hemoglobin's structural integrity (Thom et al., 2013). In Nigeria, the fungus *Auricularia auricular*—known for its therapeutic and anti-sickling properties—was shown to restore erythrocyte membrane integrity and shape due to its strong free radical scavenging abilities. This suggests its potential as a natural alternative for managing sickle cell anemia (Osunkwo et al., 2020). *Hericium erinaceus*, historically used for gastrointestinal ailments due to its polysaccharide content, has not been explored for managing chronic pain in SCD, though it may modulate heat shock proteins (HSP70), offering potential health benefits (Matthie et al., 2019).

Termite mushrooms (*Termitomyces*), native to Africa and Asia, have been used to elevate hemoglobin levels and white blood cell counts, contributing to modern medical research due to their mycelial biomass and antioxidant properties (Sadler et al., 2023; Paloi et al., 2023).

6. Conclusion

In conclusion, sickle cell disease (SCD) remains a critical global health issue, particularly in regions like Sub-Saharan Africa where its prevalence is highest. Despite significant advances in understanding the disease, including genetic underpinnings and therapeutic strategies, the management of SCD is still limited by the lack of a definitive cure and challenges related to accessibility and effectiveness of treatments. Current therapies, including blood transfusions, hydroxyurea, and hematopoietic stem cell transplantation, have been pivotal in improving patient outcomes, but further research is essential to optimize these approaches. Additionally, novel therapies targeting fetal hemoglobin expression, gene editing, and pain management offer promising avenues for the future. The role of nutrition in managing SCD, particularly in addressing deficiencies and supporting overall health, is gaining recognition, though more targeted research is needed to establish effective dietary interventions. Continued global collaboration and investment in research are crucial to improving the quality of life for individuals with SCD worldwide.

Author contributions

R.M.H.A.-R. was responsible for conceptualization, methodology, and writing the original draft. N.N.A. contributed to data curation, formal analysis, and manuscript review and editing. S.G.A.-F. provided supervision, validation, and secured funding. All authors have read and approved the final manuscript.

Acknowledgment

The authors were grateful to their department.

Competing financial interests

The authors have no conflict of interest.

References

Adigwe, O. P., Onoja, S. O., & Onavbavba, G. (2023). A critical review of sickle cell disease burden and challenges in sub-Saharan Africa. Journal of Blood Medicine, 14, 367-376.https://doi.org/10.2147/JBM.S406196

Aldakeel, S.A., Ghanem, N.Z., Al-Amodi, A.M., Osman, A.K., Al Asoom, L.I., Ahmed, N.R., Almandil, N.B., Akhtar, M.S., Azeez, S.A., & Borgio, J.F. (2020). Identification of seven novel variants in the β-globin gene in transfusion-dependent and normal patients. Archives of Medical Science, 16, 453-459.https://doi.org/10.5114/aoms.2019.84825

Ali, M. A., Ahmad, A., Chaudry, H., Aiman, W., Aamir, S., Anwar, M. Y., & Khan, A. (2020). Efficacy and safety of recently approved drugs for sickle cell disease: A review of clinical trials. Experimental Hematology, 92, 11-18.e1.https://doi.org/10.1016/j.exphem.2020.08.008

Al-Saqladi, A. W. M., Cipolotti, R., Fijnvandraat, K., & Brabin, B. J. (2008). Growth and nutritional status of children with homozygous sickle cell disease. Annals of Tropical Paediatrics, 28, 165-189.https://doi.org/10.1179/146532808X335624

Ansong, D., Akoto, A. O., Ocloo, D., & Ohene-Frempong, K. (2013). Sickle cell disease: Management options and challenges in developing countries. Mediterranean Journal of Hematology and Infectious Diseases, 5(1), e2013062.https://doi.org/10.4084/mjhid.2013.062

Arishi, W. A., Al-hadrami, H. A., & Zourob, M. (2021). Techniques for the detection of sickle cell disease: A review. Micromachines, 12(5), 519.https://doi.org/10.3390/mi12050519

Arji, E. E., Eze, U. J., Ezenwaka, G. O., & Kennedy, N. (2023). Evidence-based interventions for reducing sickle cell disease-associated morbidity and mortality in sub-Saharan Africa: A scoping review. SAGE Open Medicine, 11.https://doi.org/10.1177/20503121231197866

Arribas-López, E., Zand, N., Ojo, O., Snowden, M.J., & Kochhar, T. (2021). The effect of amino acids on wound healing: A systematic review and meta-analysis on arginine and glutamine. Nutrients, 13, 2498. https://doi.org/10.3390/nu13082498

Arruda, M.M., Mecabo, G., Rodrigues, C.A., Matsuda, S.S., Rabelo, I.B., & Figueiredo, M.S. (2013). Antioxidant vitamins C and E supplementation increases markers of haemolysis in sickle cell anaemia patients: A randomized, double-blind, placebo-controlled trial. Br. J. Haematol., 160, 688-700.https://doi.org/10.1111/bjh.12185

Bello-Manga, H., DeBaun, M. R., & Kassim, A. A. (2016). Epidemiology and treatment of relative anemia in children with sickle cell disease in Sub-Saharan Africa. Expert Review of Hematology, 9, 1031-1042.https://doi.org/10.1080/17474086.2016.1240612

Biswal, S., Rizwan, H., Pal, S., Sabnam, S., Parida, P., & Pal, A. (2019). Oxidative stress, antioxidant capacity, biomolecule damage, and inflammation symptoms of sickle cell disease in children. Hematology, 24, 1-9.https://doi.org/10.1080/10245332.2018.149844

Boadu, I., Ohemeng, A., & Renner, L. A. (2018). Dietary intakes and nutritional status of children with sickle cell disease at the Princess Marie Louise Hospital, Accra-A survey. BMC Nutrition, 4, 33. https://doi.org/10.1186/s40795-018-0241-z

Bou-Fakhredin, R., De Franceschi, L., Motta, I., Cappellini, M. D., & Taher, A. T. (2022). Pharmacological induction of fetal hemoglobin in β-thalassemia and sickle cell disease: An updated perspective. Pharmaceuticals, 15(6), 753.https://doi.org/10.3390/ph15060753

Brandow, A. M., Carroll, C. P., Creary, S., Edwards-Elliott, R., Glassberg, J., Hurley, R. W., Kutlar, A., Seisa, M., Stinson, J., Strouse, J. J., et al. (2020). American Society of Hematology 2020 guidelines for sickle cell disease: Management of acute and chronic pain. Blood Advances, 4(17), 2656-2701.https://doi.org/10.1182/bloodadvances.2020001851

Cabrera-Mulero, A., Tinahones, A., Bandera, B., Moreno-Indias, I., Macías-González, M., Tinahones, F. J. (2019). Keto microbiota: A powerful contributor to host disease recovery. Review of Endocrine and Metabolic Disorders, 20, 415-425.https://doi.org/10.1007/s11154-019-09518-8

Cairo, C., & Webb, T. J. (2022). Effective barriers: The role of NKT cells and innate lymphoid cells in the gut. Journal of Immunology, 208, 235-246.https://doi.org/10.4049/jimmunol.2100799

Colombatti, R., Hegemann, I., Medici, M., & Birkegård, C. (2023). Systematic literature review shows gaps in data on global prevalence and birth prevalence of sickle cell disease and sickle cell trait: Call for action to scale up and harmonize data collection. Journal of Clinical Medicine, 12(11), 5538.https://doi.org/10.3390/jcm12175538

Cox, S.E., Makani, J., Fulford, A.J., Komba, A.N., Soka, D., Williams, T.N., Newton, C.R., Marsh, K., & Prentice, A.M. (2011). Nutritional status, hospitalization and mortality among patients with sickle cell anemia in Tanzania. Haematologica, 96, 948-953.https://doi.org/10.3324/haematol.2010.028167

Da Guarda, C. C., Yahouédéhou, S. C. M. A., Santiago, R. P., Neres, J. S. D. S., Fernandes, C. F. D. L., Aleluia, M. M., Figueiredo, C. V. B., Fiuza, L. M., Carvalho, S. P., Oliveira, R. M. D., et al. (2020). Sickle cell disease: A distinction of two most frequent genotypes (HbSS and HbSC). PLOS ONE, 15, e0228399.https://doi.org/10.1371/journal.pone.0228399

Danton, O., Somboro, A., Fofana, B., Diallo, D., Sidibé, L., Rubat-Coudert, C., Marchand, F., Eschalier, A., Ducki, S., & Chalard, P. (2019). Ethnopharmacological survey of plants used in the traditional treatment of pain conditions in Mali. J. Herb. Med., 17-18, 100271.https://doi.org/10.1016/j.hermed.2019.100271

Darbari, D.S., Sheehan, V.A., & Ballas, S.K. (2020). The vaso-occlusive pain crisis in sickle cell disease: Definition, pathophysiology, and management. Eur. J. Haematol., 105, 237-246.https://doi.org/10.1111/ejh.13430

Darshana, T., Rees, D., & Premawardhena, A. (2021). Hydroxyurea and blood transfusion therapy for sickle cell disease in South Asia: Inconsistent treatment of a neglected disease. Orphanet Journal of Rare Diseases, 16, 148.https://doi.org/10.1186/s13023-021-01781-w

Delesderrier, E., Curioni, C., Omena, J., Macedo, C.R., Cople-Rodrigues, C., & Citelli, M. (2020). Antioxidant nutrients and hemolysis in sickle cell disease. Clin. Chim. Acta, 510, 381-390.https://doi.org/10.1016/j.cca.2020.07.020

Delgadinho, M., Ginete, C., Santos, B., Mendes, J., Miranda, A., Vasconcelos, J., & Brito, M. (2022). Microbial gut evaluation in an Angolan paediatric population with sickle cell disease. Journal of Cellular and Molecular Medicine, 26(11), 5360-5368.https://doi.org/10.1111/jcmm.17402

Dixit, R., Nettem, S., Madan, S.S., Soe, H.H.K., Abas, A.B.L., Vance, L.D., & Stover, P.J. (2018). Folate supplementation in people with sickle cell disease. Cochrane Database Syst. Rev., 2018, CD011130.https://doi.org/10.2139/ssrn.3297902

Doss, J. F., Jonassaint, J. C., Garrett, M. E., Ashley-Koch, A. E., Telen, M. J., & Chi, J. T. (2016). Phase 1 study of a sulforaphane-containing broccoli sprout homogenate for sickle cell disease. PLOS ONE, 11, e0152895.https://doi.org/10.1371/journal.pone.0152895

Dosunmu-Ogunbi, A.M., Wood, K.C., Novelli, E.M., & Straub, A.C. (2019). Decoding the role of SOD2 in sickle cell disease. Blood Adv., 3, 2679-2687.https://doi.org/10.1182/bloodadvances.2019000527

Du, M., Van Ness, S., Gordeuk, V., Nouraie, S.M., Nekhai, S., Gladwin, M., Steinberg, M.H., & Sebastiani, P. (2018). Biomarker signatures of sickle cell disease severity. Blood Cells, Molecules, and Diseases, 72, 1-9.https://doi.org/10.1016/j.bcmd.2018.05.001

Dutta, D., Methe, B., Amar, S., Morris, A., & Lim, S. H. (2019). Intestinal injury and gut permeability in sickle cell disease. Journal of Translational Medicine, 17, 183.https://doi.org/10.1186/s12967-019-1938-8

Eaton, W. A., & Bunn, H. F. (2017). Treating sickle cell disease by targeting HbS polymerization. Blood, 129(19), 2719-2726.https://doi.org/10.1182/blood-2017-02-765891

Egesa, W.I., Nakalema, G., Waibi, W.M., Turyasiima, M., Amuje, E., Kiconco, G., Odoch, S., Kumbakulu, P.K., Abdirashid, S., & Asiimwe, D. (2022). Sickle cell disease in children and adolescents: A review of the historical, clinical, and public health perspective of sub-Saharan Africa and beyond. International Journal of Pediatrics, 2022, 3885979.https://doi.org/10.1155/2022/3885979

Elendu, C., Amaechi, D.C., Alakwe-Ojimba, C.E., Elendu, T.C., Elendu, R.C., Ayabazu, C.P., Aina, T.O., Aborisade, O., & Adenikinju, J.S. (2023). Understanding sickle cell disease: Causes, symptoms, and treatment options. Medicine, 102, E35237.https://doi.org/10.1097/MD.0000000000035237

Ershler, W.B., De Castro, L.M., Pakbaz, Z., Moynahan, A., Weycker, D., Delea, T.E., Agodoa, I., & Cong, Z. (2023). Hemoglobin and end-organ damage in individuals with sickle cell disease. Current Therapeutic Research, 98, 100696.https://doi.org/10.1016/j.curtheres.2023.100696

Fernandes, T. H., & Bell, V. (2023). The imprecision of micronutrient requirement values: The example of vitamin D. Journal of Food Science, 89, 51-63.https://doi.org/10.1111/1750-3841.16889

Ferreira de Matos, C., Comont, T., Castex, M. P., Lafaurie, M., Walter, O., Moulis, G., Dion, J., Cougoul, P. (2022). Risk of vaso-occlusive episodes in patients with sickle cell disease exposed to systemic corticosteroids: A comprehensive review. Expert Review of Hematology, 15, 1045-1054.https://doi.org/10.1080/17474086.2022.2149488

Forman, H.J., & Zhang, H. (2021). Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nat. Rev. Drug Discov., 20, 689-709.https://doi.org/10.1038/s41573-021-00267-5

Galatas, B., Mabote, L., Simone, W., Matambisso, G., Nhamussua, L., Mañú-Pereira, M. D. M., Menéndez, C., Saute, F., Macete, E., Bassat, Q., et al. (2017). Heterogeneity of G6PD deficiency prevalence in Mozambique: A school-based cross-sectional survey in three different regions. Malaria Journal, 16, 36.https://doi.org/10.1186/s12936-016-1674-y

Grosse, S.D., Odame, I., Atrash, H.K., Amendah, D.D., Piel, F.B., & Williams, T.N. (2011). Sickle cell disease in Africa: A neglected cause of early childhood mortality. American Journal of Preventive Medicine, 41, S398-S405.https://doi.org/10.1016/j.amepre.2011.09.013

Habara, A., & Steinberg, M.H. (2016). Minireview: Genetic basis of heterogeneity and severity in sickle cell disease. Experimental Biology and Medicine, 241, 689-696.https://doi.org/10.1177/1535370216636726

Haroun, E., Kumar, P. A., Saba, L., Kassab, J., Ghimire, K., Dutta, D., & Lim, S. H. (2023). Intestinal barrier functions in hematologic and oncologic diseases. Journal of Translational Medicine, 21, 233.https://doi.org/10.1186/s12967-023-04091-w

Hazzazi, A. A., Ageeli, M. H., Alfaqih, A. M., Jaafari, A. A., Malhan, H. M., & Bakkar, M. M. (2020). Epidemiology and characteristics of sickle cell patients admitted to hospitals in Jazan region, Saudi Arabia. Journal of Applied Hematology, 11, 10-14.https://doi.org/10.4103/joah.joah_67_19

Hibbert, J. M., Hsu, L. L., Bhathena, S. J., Irune, I., Sarfo, B., Creary, M. S., Gee, B. E., Mohamed, A. I., Buchanan, I. D., Al-Mahmoud, A., et al. (2005). Proinflammatory cytokines and the hypermetabolism of children with sickle cell disease. Experimental Biology and Medicine, 230, 68-74.https://doi.org/10.1177/153537020523000109

Hyacinth, H. I., Gee, B. E., & Hibbert, J. M. (2010). The role of nutrition in sickle cell disease. Nutritional Metabolism Insights, 3.https://doi.org/10.4137/NMI.S5048

Inusa, B.P.D., Hsu, L.L., Kohli, N., Patel, A., Ominu-Evbota, K., Anie, K.A., Atoyebi, W. (2019). Sickle cell disease-Genetics, pathophysiology, clinical presentation and treatment. International Journal of Neonatal Screening, 5, 20.https://doi.org/10.3390/ijns5020020

Kamal, S., Naghib, M.M., Zahrani, J.A., Hassan, H., Moawad, K., & Arrahman, O. (2021). The influence of nutrition on disease severity and health-related quality of life in adults with sickle cell disease: A prospective longitudinal study. Mediterr. J. Hematol. Infect. Dis., 13, e2021007.https://doi.org/10.4084/mjhid.2021.007

Kargutkar, N., Sawant-Mulay, M., Hariharan, P., Chandrakala, S., & Nadkarni, A. (2023). Role of microRNA in hydroxyurea mediated HbF induction in sickle cell anemia patients. Scientific Reports, 13, 369.https://doi.org/10.1038/s41598-022-25444-3

Liu, Y., Su, S., Shayo, S., Bao, W., Pal, M., Dou, K., Shi, P.A., Aygun, B., Campbell-Lee, S., Lobo, C.A., et al. (2023). Hemolysis dictates monocyte differentiation via two distinct pathways in sickle cell disease vaso-occlusion. Journal of Clinical Investigation, 133, e172087.https://doi.org/10.1172/JCI172087

Matthie, N., Ross, D., Sinha, C., Khemani, K., Bakshi, N., & Krishnamurti, L. (2019). A qualitative study of chronic pain and self-management in adults with sickle cell disease. Journal of the National Medical Association, 111, 158-168 https://doi.org/10.1016/j.jnma.2018.08.001

McCormick, M., Osei-Anto, H. A., & Martinez, R. M. (2020). Addressing sickle cell disease: A strategic plan and blueprint for action. National Academies Press. Washington, DC.https://doi.org/10.17226/25632

Murad, M. H., Liem, R. I., Lang, E. S., Akl, E. A., Meerpohl, J. J., DeBaun, M. R., Tisdale, J. F., Brandow, A. M., Lanzkron, S. M., Chou, S. T., et al. (2019). 2019 sickle cell disease guidelines by the American Society of Hematology: Methodology, challenges, and innovations. Blood Advances, 3(22), 3945-3950.https://doi.org/10.1182/bloodadvances.2019000931

Nader, E., Romana, M., & Connes, P. (2020). The red blood cell-Inflammation vicious circle in sickle cell disease. Frontiers in Immunology, 11, 517556.https://doi.org/10.3389/fimmu.2020.00454

Nartey, E. B., Spector, J., Adu-Afarwuah, S., Jones, C. L., Jackson, A., Ohemeng, A., Shah, R., Koryo-Dabrah, A., Kuma, A. B. A., Hyacinth, H. I., et al. (2021). Nutritional perspectives on sickle cell disease in Africa: A systematic review. BMC Nutrition, 7, 9.https://doi.org/10.1186/s40795-021-00410-w

Ngou, C. M., Bayibéki, A. N., Abate, L., Makinde, O. S., Feufack-Donfack, L. B., Sarah-Matio, E. M., Bouopda-Tuedom, A. G., Taconet, P., Moiroux, N., Awono-Ambéné, P. H., et al. (2023). Influence of the sickle cell trait on Plasmodium falciparum infectivity from naturally infected gametocyte carriers. BMC Infectious Diseases, 23, 317.https://doi.org/10.1186/s12879-023-08134-x

Njoku, F., Zhang, X., Shah, B.N., Machado, R.F., Han, J., Saraf, S.L., Gordeuk, V.R. (2021). Biomarkers of clinical severity in treated and untreated sickle cell disease: A comparison by genotypes of a single center cohort and African Americans in the NHANES Study. British Journal of Haematology, 194, 767-778.https://doi.org/10.1111/bjh.17682

Ohemeng, A., Nartey, E. B., Quaidoo, E., Ansong, R. S., & Asiedu, M. S. (2023). Knowledge and nutrition-related practices among caregivers of adolescents with sickle cell disease in the Greater Accra region of Ghana. BMC Public Health, 23, 434.https://doi.org/10.1186/s12889-023-15343-1

Onalo, R., Cooper, P., Cilliers, A., Vorster, B.C., Uche, N.A., Oluseyi, O.O., Onalo, V.D., Zubairu, Y., Ayodele-Kehinde, A.U., Damilare, O.M., & et al. (2021). Randomized control trial of oral arginine therapy for children with sickle cell anemia hospitalized for pain in Nigeria. Am. J. Hematol., 96, 89-97.https://doi.org/10.1002/ajh.26028

Osunkwo, I., O'Connor, H.F., & Saah, E. (2020). Optimizing the management of chronic pain in sickle cell disease. Hematology, 2020, 562-569.https://doi.org/10.1182/hematology.2020000143

Paloi, S., Kumla, J., Paloi, B.P., Srinuanpan, S., Hoijang, S., Karunarathna, S.C., Acharya, K., Suwannarach, N., & Lumyong, S. (2023). Termite mushrooms (Termitomyces), a potential source of nutrients and bioactive compounds exhibiting human health benefits: A review. J. Fungi, 9, 112.https://doi.org/10.3390/jof9010112

Piel, F. B., Hay, S. I., Gupta, S., Weatherall, D. J., & Williams, T. N. (2013). Global burden of sickle cell anaemia in children under five, 2010-2050: Modelling based on demographics, excess mortality, and interventions. PLOS Medicine, 10(8), e1001484.https://doi.org/10.1371/journal.pmed.1001484

Piel, F. B., Patil, A. P., Howes, R. E., Nyangiri, O. A., Gething, P. W., Dewi, M., Temperley, W. H., Williams, T. N., Weatherall, D. J., & Hay, S. I. (2013). Global epidemiology of sickle haemoglobin in neonates: A contemporary geostatistical model-based map and population estimates. Lancet, 381(9861), 142-151.https://doi.org/10.1016/S0140-6736(12)61229-X

Piel, F. B., Rees, D. C., DeBaun, M. R., Nnodu, O., Ranque, B., Thompson, A. A., Ware, R. E., Abboud, M. R., Abraham, A., Ambrose, E. E., et al. (2023). Defining global strategies to improve outcomes in sickle cell disease: A Lancet Haematology commission. Lancet Haematology, 10(10), e633-e686.https://doi.org/10.1016/S2352-3026(23)00096-0

Quinn, C.T. (2016). Minireview: Clinical severity in sickle cell disease: The challenges of definition and prognostication. Experimental Biology and Medicine, 241, 679-688.https://doi.org/10.1177/1535370216640385

Ranque, B., Kitenge, R., Ndiaye, D. D., Ba, M. D., Adjoumani, L., Traore, H., Coulibaly, C., Guindo, A., Boidy, K., Mbuyi, D., et al. (2022). Estimating the risk of child mortality attributable to sickle cell anaemia in sub-Saharan Africa: A retrospective, multicentre, case-control study. Lancet Haematology, 9(4), e208-e216.https://doi.org/10.1016/S2352-3026(22)00004-7

Reber, E., Gomes, F., Vasiloglou, M. F., Schuetz, P., & Stanga, Z. (2019). Nutritional risk screening and assessment. Journal of Clinical Medicine, 8, 1065.https://doi.org/10.3390/jcm8071065

Reed, J.D., Redding-Lallinger, R., & Orringer, E.P. (1987). Nutrition and sickle cell disease. Am. J. Hematol., 24, 441-455.https://doi.org/10.1002/ajh.2830240416

Roy, S., Nag, S., Saini, A., & Choudhury, L. (2022). Association of human gut microbiota with rare diseases: A close peep through. Intractable and Rare Diseases Research, 11, 52-62.https://doi.org/10.5582/irdr.2022.01025

Sadeghi, A., Taherifard, E., Dehdari Ebrahimi, N., Rafiei, E., Hadianfard, F., & Taherifard, E. (2023). Effects of L-arginine supplementation in patients with sickle cell disease: A systematic review and meta-analysis of clinical trials. Health Sci. Reports, 6, e1167.https://doi.org/10.1002/hsr2.1167

Sadler, K.E., Atkinson, S.N., Ehlers, V.L., Waltz, T.B., Hayward, M., García, D.M.R., Salzman, N.H., Stucky, C.L., Brandow, A.M. (2023). Gut microbiota and metabolites drive chronic sickle cell disease pain. bioRxiv.https://doi.org/10.1101/2023.04.25.538342

Saelens, J. W., Petersen, J. E. V., Freedman, E., Moseley, R. C., Konaté, D., Diakité, S. A. S., Traoré, K., Vance, N., Fairhurst, R. M., Diakité, M., et al. (2021). Impact of sickle cell trait hemoglobin on the intraerythrocytic transcriptional program of Plasmodium falciparum. mSphere, 6(2), e0075521.https://doi.org/10.1128/mSphere.00755-21

Sahu, T., Pande, B., Verma, H.K., Bhaskar, L.V.K.S., Sinha, M., Sinha, R., & Rao, P.V. (2023). Infection and potential challenge of childhood mortality in sickle cell disease: A comprehensive review of the literature from a global perspective. Thalass. Rep., 13, 206-229.https://doi.org/10.3390/thalassrep13030019

Sesethu, G., Nombalentle, M., Yamkela, M., Anelisa, M., Makumire, S., Mkwetshana, N., Govender, K. K., Makhoba, X. H. (2023). In silico evaluation of heat shock proteins reveals an interplay with polyamines as a survival strategy for Plasmodium falciparum. INNOSC Theranostics Pharmacological Science, 1228.https://doi.org/10.36922/itps.1228

Soe, H. H. K., Abas, A. B. L., Than, N. N., Ni, H., Singh, J., Said, A. R. B. M., & Osunkwo, I. (2020). Vitamin D supplementation for sickle cell disease. Cochrane Database of Systematic Reviews, 5, CD010858.https://doi.org/10.1002/14651858.CD010858.pub3

Stuart, M.J., & Nagel, R.L. (2004). Sickle-cell disease. Lancet, 364, 1343-1360.https://doi.org/10.1016/S0140-6736(04)17192-

Takaoka, K., Cyril, A.C., Jinesh, S., & Radhakrishnan, R. (2020). Mechanisms of pain in sickle cell disease. British Journal of Pain, 15, 213-220.https://doi.org/10.1177/2049463720920682

Tebbi, C.K. (2022). Sickle cell disease, a review. Hemato, 3, 341-366.https://doi.org/10.3390/hemato3020024

Teixeira, T. V., Da Silva, A. C. F., Rodrigues, C. D. S. C., Brito, F. D. S. B., Canella, D. S., & Citelli, M. (2023). Food consumption of people with sickle cell anemia in a middle-income country. Nutrients, 15, 1478.https://doi.org/10.3390/nu15061478

Telen, M. J., Wun, T., McCavit, T. L., De Castro, L. M., Krishnamurti, L., Lanzkron, S., Hsu, L. L., Smith, W. R., Rhee, S., Magnani, J. L., et al. (2015). Randomized phase 2 study of GMI-1070 in SCD: Reduction in time to resolution of vaso-occlusive events and decreased opioid use. Blood, 125, 2656-2664.https://doi.org/10.1182/blood-2014-06-583351

Thom, C.S., Dickson, C.F., Gell, D.A., & Weiss, M.J. (2013). Hemoglobin variants: Biochemical properties and clinical correlates. Cold Spring Harbor Perspectives in Medicine, 3, a011858.https://doi.org/10.1101/cshperspect.a01185

Thomson, A.M., McHugh, T.A., Oron, A.P., Teply, C., Lonberg, N., Vilchis Tella, V., Wilner, L.B., Fuller, K., Hagins, H., Aboagye, R.G., et al. (2023). Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: A systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematology, 10, e585-e599.https://doi.org/10.1016/S2352-3026(23)00118-7

Thursby, E., & Juge, N. (2017). Introduction to the human gut microbiota. Biochemical Journal, 474, 1823-1836.https://doi.org/10.1042/BCJ20160510

Townsend, J. R., Kirby, T. O., Marshall, T. M., Church, D. D., Jajtner, A. R., & Esposito, R. (2023). Foundational nutrition: Implications for human health. Nutrients, 15, 2837.https://doi.org/10.3390/nu15132837

Uçucu, S., Karabıyık, T., & Azik, F. (2022). Difficulties in the diagnosis of HbS/beta thalassemia: Really a mild disease? Journal of Medical Biochemistry, 41, 32-39.https://doi.org/10.5937/jomb0-30420

Umeakunne, K., & Hibbert, J. M. (2019). Nutrition in sickle cell disease: Recent insights. Nutritional Dietetics and Supplements, 11, 9-17.https://doi.org/10.2147/NDS.S168257

Venugopal, A., Chandran, M., Eruppakotte, N., Kizhakkillach, S., Breezevilla, S.C., & Vellingiri, B. (2018). Monogenic diseases in India. Mutation Research, 776, 23-31.https://doi.org/10.1016/j.mrrev.2018.03.003

Ware, R. E. (2015). Optimizing hydroxyurea therapy for sickle cell anemia. Hematology, 2015, 436-443.https://doi.org/10.1182/asheducation-2015.1.436

Williams, T. N., Mwangi, T. W., Wambua, S., Alexander, N. D., Kortok, M., Snow, R. W., & Marsh, K. (2005). Sickle cell trait and the risk of Plasmodium falciparum malaria and other childhood diseases. Journal of Infectious Diseases, 192(1), 178-186.https://doi.org/10.1086/430744

Yenilmez, E. D., & Tuli, A. (2016). New perspectives in prenatal diagnosis of sickle cell anemia. In B. P. D. Inusa (Ed.), Sickle cell disease pain and common chronic complications (pp. 315-328). IntechOpen.https://doi.org/10.5772/64646

Yin, R., Kuo, H. C., Hudlikar, R., Sargsyan, D., Li, S., Wang, L., Wu, R., & Kong, A. N. (2019). Gut microbiota, dietary phytochemicals, and benefits to human health. Current Pharmacology Reports, 5, 332-344.https://doi.org/10.1007/s40495-019-00196-3

Zemel, B. S., Kawchak, D. A., Fung, E. B., Ohene-Frempong, K., & Stallings, V. A. (2002). Effect of zinc supplementation on growth and body composition in children with sickle cell disease. American Journal of Clinical Nutrition, 75, 300-307.https://doi.org/10.1093/ajcn/75.2.300

Zhao, L. Y., Mei, J. X., Yu, G., Lei, L., Zhang, W. H., Liu, K., Chen, X. L., Kołat, D., Yang, K., & Hu, J. K. (2023). Role of the gut microbiota in anticancer therapy: From molecular mechanisms to clinical applications. Signal Transduction and Targeted Therapy, 8, 201.https://doi.org/10.1038/s41392-023-01406-7

Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. Cell Research, 30, 492-506.https://doi.org/10.1038/s41422-020-0332-7

PMid:32433595 PMCid:PMC7264227