Int J Biol Med Res. 2024; 15(3): 7849-7853

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Review Article

An Overview of Sickle Cell Disease from an Immunological Perspective

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ARTICLEINFO

Keywords:
Sickling Test
Sickle Cell Anaemia
Immune Cells

ABSTRACT

Sickle Cell Disease is a genetic mutation in the haemoglobin gene which results in chronic hemolytic anaemia and progressive damage to multiple organs that affect the immune system. However, little is known about how this disease affects the adaptive immune response. This paper offers a summary of sickle cell disease from an immunological standpoint. PRISMA-compliant electronic articles from Google Scholar, PubMed, Research Gate, and Scopus were obtained by searching for terms like "immunological cells," "red blood cells," and "white blood cells." The findings of this study indicate that persons with sickle cell anaemia are more prone to infection and inflammation due to the damage that might occur to their irregularly shaped red blood cells. Bone marrow and stem cell transplantation have been shown to be among the best strategies to treat sickle cell disease holistically. While new medications are being created, more research must be done to understand how the immune system, in particular the adaptive immune system to rectify this aberration.

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Introduction

Sickle Cell Anaemia, usually referred to as sickle cell disease (SCD), is a global health concern that impacts millions of individuals, primarily those with African, Mediterranean, Middle Eastern, and Indian ancestry [1]. Over 300,000 kids are born with sickle cell disease every year throughout the world. Nigeria is one of the most affected countries, producing roughly 150,000 SCD babies annually, with 70–90% of deaths occurring before the child is five years old [2]. People who have sickle cell anaemia frequently struggle with a variety of health issues, such as persistent pain, exhaustion, an increased risk of infections, organ damage, , as well as consequences like acute chest syndrome or stroke [3,4,5]. Because of the condition's impact on their day-to-day existence, they could have emotional and social difficulties. Dactylitis, for instance, is more common in youngsters, although heart failure and chronic leg ulcers are more common in adults [6]. Strokes can also occur in children, which can impair brain function, impair academic achievement, and account for long-term cognitive function deficits in adults, which can show up as ineffective pain management or noncompliance with treatment recommendations [7].

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It also poses a number of difficulties, such as restricted access to high-quality medical care, a dearth of specialized treatment facilities, and a dearth of knowledge and instruction on condition [8]. Misconceptions and social stigmatization of the illness could also exist. The cause of sickle cell disease. Misconceptions and social stigmatisation of the illness could also exist. In haemoglobin S, sickle cell disease results in the synthesis of aberrant beta-chains [2,9]. Low oxygen concentration fallouts cause haemoglobin S (HbS) to polymerise, resulting in sickle-shaped red blood cells that are stiff and have a shortened life span [10]. This change in one DNA base can have a cascading effect on several organs and systems, resulting in physiological repercussions 3. Vasculopathy, a disease of the blood vessels, and a number of additional problems are the result of these processes 2,3. Recent studies have revealed the role of the immune system, particularly the innate immune system, in the pathophysiology of sickle cell disease (SCD) [2, 10]. However, little is known about how the adaptive immune system functions in this illness.

MATERIAL AND METHOD

This article examines how blood transfusions, oxidative stress, inflammation, and the immune system interact with sickle cell anaemia. Supplies and Procedures Using search themes like "immunological cells," "red blood cells," "white blood cells," and "Sickle Cell Anaemia," published publications in electronic databases like Google Scholar, PubMed, Research Gate, and Scopus were retrieved for this review.

Criteria for Inclusion and Exclusion

The PRISMA paradigm was followed in documenting the reason for exclusion at the full-text screen level [11]. Using the EndNote application, duplicate research from several electronic databases that were found through the search technique were eliminated. After that, the full-text copies of the qualified articles were obtained and examined to see if they satisfied the requirements for inclusion.

Sickle Cell Anaemia

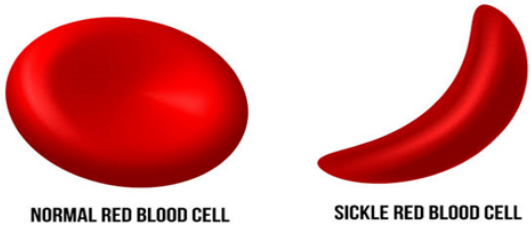


Figure 1 Red blood cells that are sickled and normal [12]

A genetic mutation in the haemoglobin gene causes sickle cell anaemia, which inhibits normal blood flow and results in chronic hemolytic anaemia, recurrent symptoms, and gradual damage to many organs]4, 13]. Normal red blood cells have a disc shape and are flexible enough to fit through even the tiniest blood vessels [14]. The sickle-shaped red blood cells (RBCs) in sickle cell disease (SCD) transform the normally flexible disc into rigid, sticky sickle cells that obstruct blood flow [14,15]. An individual inherits one mutant copy of the β-globin gene from each parent to cause this autosomal recessive condition [10]. Typically, parents who possess the sickle trait do not exhibit any disease-related phenotypes or symptoms [16]. Sickle cell anaemia has been around for a very long time. It was first recognised as a clinical condition in western medicine in 1910 when a doctor by the name of James Herrick discovered irregularly shaped red blood cells in a patient's blood sample [17]. Herrick was the first to write a case report on the illness. The World Health Organisation (WHO) declared it to be a global health issue in 2006. Band-3, ankyrin, and spectrin are examples of cytoskeletal proteins that are altered when abnormal globin chains accumulate along the cell membrane. Red cell volume regulation, transmembrane anion transport, structural cytoskeletal organisation, and CO2 elimination all depend on Band-3 [18]. SCD was verified during the initial during the first year of life, primarily during the first five months of age [19–20], SCD was confirmed. While there is currently no known cure for sickle cell anaemia, therapies like bone marrow transplants and transfusions may be able to help manage symptoms while also advancing our knowledge of the disease's pathogenesis and genetics [21]. SCA damages different body organs, raises inflammation, and reduces oxygen delivery [3].

Sickle Cells and the Immune System

Figure 2. The immune system and sickle cells [22].

Because sickle cell anaemia can cause the spleen to shrink and become damaged over time, those who have the condition may have impaired spleen function. The spleen plays a vital role in the immune system, its malfunction as a result of sickle cell anaemia makes a person more susceptible to illnesses like meningitis and pneumonia [14]. Sickle cell anaemia is caused by a variety of immune cell types. Among them are:

1. White blood cells: A sickness may cause a decrease in these cells, which aid in the defence against infections. White blood cells of various kinds, such as neutrophils, lymphocytes, monocytes, and eosinophils, are implicated in sickle cell anaemia [15]. Leukocytes aid in the defence against bacterial infections. When sickle cell crises occur, neutrophils are essential because they target and eliminate damaged red blood cells from the bloodstream. Furthermore, they aid in the prevention of infection by identifying and eliminating microorganisms that might have infiltrated the body as a result of tissue damage sustained during an emergency [15]. Neutrophils are essential for controlling sickle cell disease symptoms because of these roles. Cancerous cells and virus-infected cells are the targets of lymphocytes. In sickle cell crises, lymphocytes play a crucial role in identifying and eliminating germs and viruses that may have infiltrated the body as a result of tissue damage sustained during the crisis [15]. Furthermore, lymphocytes have a part in controlling immunological responses, which can lessen the risk of sickle cell disease consequences. All things considered, lymphocytes and neutrophils play crucial roles in the immune system's reaction to sickle cell disease emergencies. Monocytes play a crucial role in eliminating damaged or dead cells from the body because monocytes have the capacity to mature into macrophages, which aid in the body's removal of damaged red blood cells, they are crucial during sickle cell crises. Moreover, they generate cytokines, which control the inflammatory response in times of emergency [15]. Monocytes are crucial for controlling sickle cell disease symptoms and averting consequences that can arise if left untreated [15].

Eosinophils are important in the management of allergies and parasitic infections, although they are not usually engaged in sickle cell crises. There might be fewer white blood cells overall, though, because sickle cell anaemia affects the immune system]15].

2.Macrophages: By eliminating damaged red blood cells from circulation and different chemicals involved in inflammation, macrophages have a significant impact on sickle cell anaemia. By consuming and dissolving the aberrant, malformed cells, these macrophages can lessen inflammation and prevent obstructions in tiny blood arteries. On the other hand, oxidative stress and altered immunological signalling can potentially affect macrophage activity in sickle cell anaemia patients. This could exacerbate the disease's side effects, like organ damage and heightened infection susceptibility [15].

Difficulties and Exposure to the Sickled cell

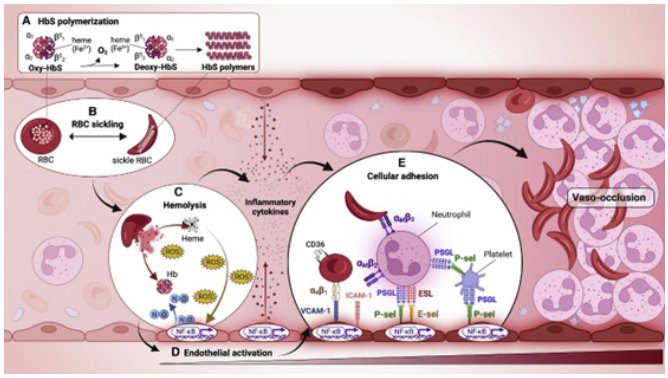


Figure 3 Vascular blockage in sickle cell illness [23].

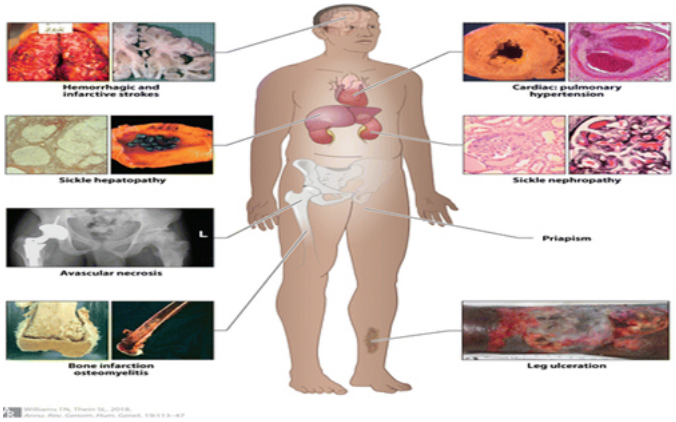
A number of problems are possible with sickle cell anaemia. Among the most prevalent is pain, which can be either acute or chronic and is frequently brought on by vaso-occlusive events or sickle cell crises [2,3]. Additional risks include pulmonary hypertension, anaemia brought on by the breakdown of red blood cells, stroke brought on by a reduction in the brain's oxygen supply, and damage to other organs, especially the liver, kidneys, and eyes [2]. Avascular necrosis of bone tissue, osteomyelitis, delayed puberty, infertility, priapism, delayed growth, and leg ulcers are among the other conditions that sickle cell anaemia patients may encounter [4].

Patients with sickle cell disease may experience a range of psychological, social, and environmental difficulties. Because their condition is persistent, individuals may have emotional problems such as anxiety, sadness, and even post-traumatic stress disorder in addition to numerous hospital stays. Socially, sickle cell patients may experience stigma or prejudice because of their condition, or they may find it difficult to get the right care because of regional variations in healthcare. Sickle cell disease is more prevalent in some areas due to environmental factors, and these areas frequently lack sufficient healthcare resources, which causes delays in diagnosis and treatment. All things considered, having sickle cell anaemia necessitates a tremendous degree of fortitude from the patient and those around them. It's critical that friends and family treat them with empathy and, when needed, offer education and sincere emotional support [6].

Immunological Mechanism

Complications [24] Patients with sickle cell disease (SCA) may be more susceptible to infections due to compromised immune systems. They might have low blood pressure, impaired organ function, or in rare circumstances, even cognitive impairment [18]. These elements, together with frequent hospital stays brought on by crisis episodes, make it extremely for sickle cell patients and caregivers alike. It is critical that these individuals receive prompt medical attention and care while being properly supervised by

Figure 4 Sickle Cell



medical specialists. Patients with sickle cell anaemia may be more vulnerable to many infections, such as fungal infections, parasitic diseases like malaria, viral infections like influenza, hepatitis B and C, and HIV, and bacterial infections like pneumonia and meningitis. Malaria can strike people who have sickle cell anaemia [9].

Anaemia of Sickle Cells and Inborn Immunity

The term "innate immunity" describes the body's first lines of defence against infections or other external chemicals. Because of reduced immune systems and persistent inflammation brought on by the degeneration of red blood cells, innate immunity may be affected in sickle cell anaemia [2]. Patients may become more susceptible to infections as a result, and problems may become more likely. Illnesses associated to infections can worsen and innate immunity can be adversely affected by sickle cell anaemia [5].

Furthermore, sickle cells' weaker membranes allow them to rupture more easily, releasing free heme into the bloodstream. Low serum levels of complement component also make it difficult for macrophages to phagocytose sickle cells, which weakens the body's innate defence response to pathogens as a whole [13]. This considerably reduces one's capacity to successfully fight off bacterial and viral infections, which raises the morbidity and death rates among victims.

Sickle Cell Anaemia and Adaptive Immunity

SCA influences adaptive immunity in addition to the innate immune system. A 2014 study discovered that compared to healthy persons, those with sickle cell anaemia had lower antibody responses to vaccinations, suggesting a weakness in their adaptive immune system [2]. In addition, SCA results in cellular immune impairment, T cell malfunction, and persistent inflammation.

The adaptive immune system's T cells are able to identify and react to particular antigenic infections. Furthermore, depending on their role, T cells can differentiate into a variety of kinds, including regulatory T cells, cytotoxic T cells, and helper T cells [15]. Whereas cytotoxic T cells kill malignant or infected host cells directly, helper T cells stimulate other immune response mechanisms. Once infections have been eradicated, regulatory T cells inhibit the immune system to stop autoimmune reactions against healthy host tissues.

When these immune responses are triggered, malignant or infected host cells are destroyed, stopping infections from proliferating inside the body. All things considered, optimal adaptive immunity against infections and disease depends on an efficient cellular response. Consequently, sickle cell anaemia may have an impact on the effectiveness of adaptive immune responses against pathogens in addition to impairing innate immunity [14].

Making the diagnosis of sickle cell anaemia High-performance liquid chromatography, Hb electrophoresis, and complete blood cell counts are the most popular techniques for identifying sickle cell anaemia (HPLC). These techniques are regarded as the industry norm for SCD diagnosis [9].

Figure 5 Diagnosis of sickle cell anemia [25].



1. Total blood cell count: One test used to identify sickle cell anaemia is the complete blood cell count, or CBC. It gauges the concentrations of platelets, white blood cells, and other blood cell types. People who have homozygous SS and heterozygous S/β° mutations typically exhibit low red blood cell counts, haemoglobin levels, and hematocrit, a condition known as hemolytic anaemia. Furthermore, there is an elevation and variability in the white blood cells (WBC) and platelets [9].

2. Peripheral blood smear: When an anomaly in the automated counts is detected, a peripheral blood smear (PBF) is frequently performed. This entails drawing a tiny blood sample and analysing it under a microscope. Examining the blood cells on the smear, medical professionals can recognise the distinctive sickle-shaped red blood cells that are associated with sickle cell anemia [9,12].

3. The solubility sickling test entails combining a tiny volume of blood with a solution and determining if, given specific circumstances, the red blood cells "sickle," or clump together. These days, the solubility test is widely employed. It is predicated on the idea that Hb-S is insoluble in concentrated phosphate buffer, sodium dithionate, and a hemolyzing agent. These substances induce the HbS to crystallise and precipitate the cells, which refract light and muddy the solution. Both positive and negative controls are used to compare the results [9].

4. Haemoglobin Electrophoresis: This test aids in determining the various haemoglobin types present in blood. It has the ability to identify aberrant haemoglobin with precision, including haemoglobin S linked to sickle cell anaemia.

Studies using haemoglobin electrophoresis-based approaches have demonstrated low accuracy after a transfusion due to the presence of the donor's haemoglobin or during the neonatal period due to the presence of foetal haemoglobin. According to some real-world study done on Congolese SCA patients, anaemia is the most typical symptom and frequently the initial one. Because of this, individuals with suspected SCA typically have a recent history of transfusion, which forces medical professionals to postpone the diagnostic test for three months. It is typical for these children to return to the hospital and receive another transfusion within the next three months due to other underlying factors, such as malaria and other infections, which are very common in this setting. This further delays haemoglobin electrophoresis-based methods for SCA confirmation. Therefore, regardless of a recent transfusion or neonatal period, a reliable diagnostic test for SCA should maintain high accuracy [26].

5. Isoelectric Focusing (IEF): This test uses the electrical charge of haemoglobin to distinguish and identify distinct forms of haemoglobin, such as haemoglobin HbS and HbD, HbG and HbC, HbE and HbO, and HbA and HbF. By separating haemoglobin species with high precision based on their isoelectric points on gel medium, it is the most efficient method of detecting hemoglobinopathies in babies. The Hb variant migrates along the pH gradient until it reaches a net charge of zero. A clear division is attained [27].

6. High Performance Lipid Chromatography (HPLC): This method aids in the separation and examination of various haemoglobin types according to their molecular properties. Manoj et al.'s research findings [28] revealed that SCA patients had higher HbF concentrations, and it's believed a key

element in protecting patients from problems.
Increased HbA2, which indicates the presence of the β-thalassemia trait, was also discovered in this area, and it is suspected when the value is >3.7%. Therefore, ion exchange HPLC is ideal for routine hemoglobinopathies research due to its high resolution, short test time, and precise quantification [27].

7. Genetic Testing: This involves analyzing a person's DNA to detect specific genetic changes that are associated with the condition. By identifying mutations in the HBB gene, which codes for the hemoglobin protein, gene testing can provide a definitive diagnosis of sickle cell anemia [9]. Previous studies have proven that DNA-based tests are not affected by transfusions or fetal hemoglobin. However, DNA-based tests would be preferable in a resource-limited setting. The implementation of these techniques has to address underlying challenges for sample collection, transfer, and cold chain requirements for storage, as well as test accuracy in the neonatal period and following a recent transfusion [26].

Potential Treatments

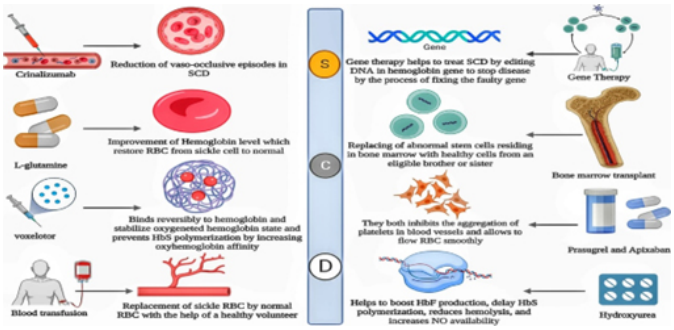


Figure 6. SCA Treatment Evolution [20]

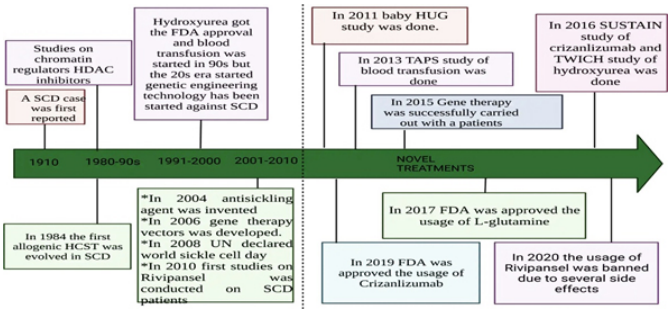


Figure 7. Potential treatment for Sickle cell anaemia [20]

There are currently several potential treatment options for sickle cell anemia. This includes, but is not limited to: 1. Crinalizumab 2. Voxelotor 3. Apixaban and Prasugrel; 4. Hydroxyurea Therapy; 5. Stem cell or bone marrow transplant 6. Gene therapy 7. Intravenous fluids/blood transfusion 8. L-glutamin. Hydroxyurea therapy can help reduce the frequency and severity of pain crises while also improving the overall quality of life for patients. In order to keep red blood cells from malforming and clogging blood arteries, it entails taking medication to boost the development of foetal haemoglobin in red blood cells [1]. Research conducted on animals suggests that the drug be stopped when pregnant; nevertheless, it is unknown how hydroxyurea would affect the developing foetus and pregnancy. When administered correctly and under medical supervision, hydroxyurea therapy is thought to be safe and has been demonstrated to be beneficial in numerous cases. An additional therapy option for sickle cell anaemia is bone marrow or stem cell transplantation [1,29]. In order to restore normal red blood cell production, this method replaces a patient's bone marrow with that of a healthy donor 20. Patients with sickle cell anaemia may benefit in the long run from it in terms of symptom management and the course of their disease, but there are risks and complications involved, including the possibility of graft-versus-host disease, which develops when newly formed bone marrow leukocytes attack target tissue cells, and immune system rejection of the transplanted cells. When a donor and recipient have compatible Human Leukocyte Antigen (HLA), graft versus host disease (GVHD) is rare; on the other hand, GVHD is more common when the two are unrelated or have different HLA types [20]. As a result, each patient's particular circumstances must be carefully considered when determining if stem cell transplantation is the appropriate course of action. Additionally, techniques for gene therapy are being investigated as these treatments seek to modify or replace the defective genes that cause the illness in an effort to enhance symptom management and the course of the disease over the long run [18]. Before these medicines are made generally accessible, further research is necessary to properly understand their efficacy and safety. While several gene therapies have demonstrated encouraging outcomes in clinical trials, more research is required to assess their long-term effectiveness and potential side effects. Because dehydration increases the likelihood that red blood cells will take on the shape of a sickle, intravenous fluids are used for rehydration to aid in the red blood cells' return to normal [14]. Additionally, blood transfusion enhances the delivery of nutrients and oxygen. Packed red blood cells are taken out of donated blood and supplied to the patient as needed. Raising the blood oxygen load capacity while lowering the risk of problems associated to vaso-occlusion is the goal of blood transfusion. Since immunity is declining, vaccination can aid in the prevention of infection [4,14].

Comprehensive Care is Important

For those with SCA, comprehensive care is crucial. In order to meet the patient's physical, emotional, and social needs, a group of medical specialists must collaborate. For example, routine physical examinations, dietary advice, and education regarding the condition and available therapies [29]. Individualized care tailored to each patient's needs could help patients with SCA enjoy longer, better lives.

CONCLUSION

The human race has been and continues to be threatened by sickle cell anaemia. Every day, adults and children pass away too soon as a result. The impacted people experience what are known as crises, which can occasionally result in mortality if they are not appropriately and quickly managed. Parents sometimes show less concern for their children's accusations against them. It is crucial to recognise that a person with Sickle Cell Disease, or "Sickler " can live a long and healthy life if everyone does their share and recognises that there is more to this genetic blood ailment than simply the present crisis.

Acknowledgment: The authors acknowledge Dr. Simon Peter Abriba for proof reading the write up and comments.

Conflict of Interest: Nothing to declare.

Funding statement: None.

Ethical approval: Not applicable.

Authors' Contribution: All authors were equally involved in literature search, review, analysis, manuscript preparation, revision and finalization.

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