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MECHANISMS, MANIFESTATIONS, DIAGNOSIS AND EMERGING TREATMENTS OF SICKLE CELL DISEASE: A COMPREHENSIVE REVIEW

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Abstract

A single point mutation in the β-globin gene results in sickle cell disease, a hereditary hemoglobinopathy that produces aberrant hemoglobin S (HbS). Sickled hemoglobin polymerizes when it is deoxygenated. Normal red blood cells become sickled as a result of this mutation. Sickle cell disease leads to several clinical complications like chronic pain crises, anemia, acute and chronic chest syndrome, stroke, vaso-occlusion, organ damage and other life-threatening health concerns. Globally, sickle cell disease affects more than 7 million people significantly in Sub-Saharan Africa, also in India and the Middle East. Disease severity is influenced by fetal hemoglobin (HbF) levels. While hydroxyurea treatments have traditionally helped the increasing fetal hemoglobin levels to cure sickle cell disease. Recent studies show that novel pharmacologic agents and other gene-based therapies like selective allogeneic hematopoietic stem cell transplantations, CRISPR-Cas9 genome editing also help to cure this disease. This review summarizes the latest evidence on molecular basis, pathophysiology, clinical manifestations and relative evolving therapeutic strategies of sickle cell disease, highlighting the recent progress and challenges in improving patient outcomes worldwide.

Introduction

Sickle cell disease is one of the most prevalent monogenic hemoglobinopathy that is inherited across worldwide. It is brought on by a single nucleotide substitution (Glu6Val) in β-globin gene (point mutation). When oxygen levels are low, this mutation produces sickle hemoglobin (HbS), which polymerizes and gives red blood cells a sickle shape. These deformed cells lead to recurrent vaso-occlusive crises (VOCs) and ultimately organs damage. Because HbS containing erythrocytes undergo hemolysis, have short life span and obstruct microvascular flow (Brandow & Liem, 2022; Taher et al., 2025).

The individuals that carry only one copy of the mutation are asymptomatic carriers (sickle cell trait), while homozygous individuals experience severe form of SCD that is sickle cell anemia (Brandow & Liem, 2022).

More than 7 million individuals with SCD suffer across worldwide, with sub-Saharan Africa, India, and the Middle East having more prevalence. It is a major health problem as, above 500,000 affected babies are born every year, particularly in regions with limited healthcare resources. Despite of advancements in early detection and supportive care, many patients still face life threatening complications and childhood mortality is also still high in areas with limited resources (Colombatti et al., 2022; Thomson et al., 2023).

Because the carriers of sickle cell trait historically had a survivability benefit over severe malaria, geographic distribution of SCD reflects evolutionary selection (Thomson et al., 2023).

Including recurrent VOCs, chronic hemolytic anemia, acute chest syndrome, stroke, splenic dysfunction, kidney damage, and leg ulcers are the

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clinical complications of SCD. Genetic modifiers like fetal hemoglobin (HbF) levels, co-inherited α-thalassemia, and polymorphisms affecting inflammation and adhesion pathways play role in variations for disease severity (Kabrah, 2025).

Environmental factors and access to healthcare also contribute to the influence disease severity among SCD patients (Metaferia et al., 2022).

Chronic anemia contributes to fatigue, delayed growth, and increased susceptibility to infection but vaso-occlusion is the main emergency cause of hospitalization and impacting quality of life badly (Onimoe & Rotz, 2020).

Traditionally, hydroxyurea has been used as the main disease-modifier therapy, because it increases HbF levels and reduce the frequency of VOCs (Rico-Mendoza et al., 2025). Novel pharmacologic therapies each of them targeting distinct pathophysiological mechanisms such as L-glutamine, voxelotor and crizanlizumab, were being introduced in last five years. Early clinical trials of gene-based therapies have been shown that are beneficial. These including exagamglogene autotemcel that lowers painful episodes and increases hemoglobin levels, are providing hope for functional cure (Kabrah, 2025).

Even after all these advancements, there are still problems like therapy accessibility, cost and response variability among many patient populations. In short, sickle cell disease is intricate, multi-system blood disorder with many clinical complications that are impacted by both genetic and environmental variables. Recent pharmacologic and gene-based strategies are reshaping the therapeutic landscape even though the traditional therapies have increased survival chances and decreased complications. It is important and also the need of understanding molecular mechanisms, global burden of SCD and recent advancements to improve the future prospects and studies for the betterment of SCD patients and management (Brandow & Liem, 2022; Colombatti et al., 2022; Menshawey & Menshawey, 2024; Thomson et al., 2023).

Global burden of sickle cell disease

SCD is widespread globally but is most common in Sub-Saharan Africa where majority of cases reported are present in its severe form, homozygous hemoglobin S disease (Colombatti et al., 2022; Payne et al., 2020).

Approximately 300,000 newborns are being diagnosed every year with SCD in Sub-Saharan Africa but its high occurrence has also been observed in India (Alabed et al., 2023; Ally & Balandya, 2023). From 2000-2021, incidence rates of SCD across the country (SSA) were comparatively consistent but because of increase in population number in Caribbean and western and central Sub-Saharan Africa, the total births of infants with sickle cell disease rose globally by 13.7, reaching 515,000 (Thomson et al., 2023).

The number of SCD patients globally increased by 41.4% (38.3-44.9) from 5.46 million (4.62-6.45) in 2000 to 7.74 million (6.51-9.2) in 2021. According to estimates of 34400 (25000-45200) leading causes of deaths in all ages worldwide in 2021, the overall SCD mortality burden was approximately 11 times greater at 376000 (Colombatti et al., 2022; Payne et al., 2020).

In Pakistan, many regional studies show the high burden of hemoglobinopathies with notably elevated prevalence, reported in major cities like Karachi and Islamabad. Approximately 2% population in Pakistan is affected with SCD every year (Khan et al., 2025).

According to GBD's 2021 estimates, there were 81100 (58800-108000) fatalities among children under the age of five, ranking total SCD mortality as 12th (compared to 40th for cause-specific SCD mortality). These trends collectively highlight the fact that SCD remains a major and deeply under-recognized global health challenge, particularly for young children in region of high burden (Alabed et al., 2023; Ally & Balandya, 2023; Oron et al., 2020; Thomson et al., 2023).

Genetic and molecular basis

Sickle cell disease and its variants are severe monogenic hemoglobinopathies that are inherited in an autosomal recessive Mendelian pattern. SCD results from a point mutation (single nucleotide substitution) in HBB gene (Huang et al., 2022).

Although there are various genotypes of sickle cell disease (SCD), 60–70% of cases are caused by HbSS (sickle cell anemia), which is more common due to inheritance of two copies of the HbS mutation.

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Sickle cell anemia (SCA, MIM: 603903) is caused by the sickle-cell gene variant [HBB; c.20A>T, p.Glu6Val; OMIM: 141900 (HBB-βS)] (Newby et al., 2021).

Hemoglobin SC (HbSC), sickle hemoglobin β0 thalassemia, and sickle hemoglobin β+ thalassemia are examples of compound heterozygous mutations that arise from the coinheritance of genes that cause other abnormal forms of hemoglobin (such HbC or β-thalassemia) with HbS (Brandow & Liem, 2022; Ballas & Darbari, 2020).

A single base pair mutation in the HBB gene causes hemoglobin S (HbS), which encodes for the adult hemoglobin's beta-globin chain. HBB gene is precisely located on short arm of chromosome 11 (p15.4) (Brandow & Liem, 2022). The HbS allele (βS), is caused by point mutation in sixth codon of the coding strand of HBB gene where a single nucleotide substitution of adenine (A) to thymine (T) occurs, changing codon sequence from GAG → GTG. This A→T substitution causes mRNA to encode for valine instead of glutamic acid (Glu→ Val) in β-globin chain of hemoglobin. This leads to (sickle) βS-globin chains within the hemoglobin tetramers (HbS). In individual with SCA the hemoglobin tetramers are consist of two normal α-chains and two sickle β-chains (α2β2S) (Sharma et al., 2023).

HbS tetramers undergo polymerization under deoxygenated conditions and form long rigid fibers. This polymerization changes the morphology of erythrocytes into sickled shape and promotes vaso-occlusion, hemolysis, and infections causing repetitive acute pain, tissue damage, strokes, may lead to multiple organs damage, or even death occurs in most of the severe cases (Brandow & Liem, 2022; Sanchez-Villalobos et al., 2022).

Overall, variations in the mutations across SCD genotypes show that disease severity and clinical outcomes depend directly upon specific hemoglobin combination inherited (Brandow & Liem, 2022; Huang et al., 2022; Sanchez-Villalobos et al., 2022; Sharma & Brandow, 2020).

Sickle hemoglobin (HbS) polymerization and red blood cells Pathomechanics

The sickle-hemoglobin (HbS) molecule is prone to form rigid, long and stiff polymers in low oxygen levels due to β-globin (Glu6Val) mutation (Sharma et al., 2023). This mutation creates a hydrophobic site that enables intermolecular contacts. At first, the sickling of RBCs is partly reversible and cyclic, with sickled red blood cells shuttling between the aberrant crescent shape which formed under low oxygen tension and the normal biconcave shape after reoxygenation (Desai et al., 2024; Huang et al., 2022).

The sickle erythrocytes ultimately take on an irreversible sickle form, which raises the risk of hemolysis and vaso-occlusion (Holdford et al., 2021), as the repeated cycles of deoxygenation shorten the polymer delay time. Modern functional studies reveal that even after reoxygenation, red blood cells that contain HbS polymer remain stiff and rigid as before. This shows that polymer accumulation has prolonged biomechanical consequences (Williams & Wood, 2023).

The pathophysiology that causes the HbS component to polymerize is shared by all SCD variations, even though the range of polymer formation varies with total HbS concentration and co-inherited modifiers. Among the factors that lead to deoxygenation, which promotes HbS polymerization during hypoxia, are physiologically high 2, 3-diphosphoglycerate and increased sphingokinase-1 activity (Suhail, 2024).

HbS polymerization is further increased by a high quantity of HbS, Aberrant Gardos channel activity (KCNN4) leads to loss of K+, dehydration, and recurrent injury to the membrane of red blood cells (RBCs). By auto-oxidizing HbS, oxidative stress causes hemolysis and damages the membrane of erythrocyte cells (Williams & Wood, 2023).

In sickle red blood cells (RBCs), the oxidative stress is increased by the elevated expression of xanthine oxidase and xanthine dehydrogenase. Recent microfluid hypoxia studies show that RBCs having stiff polymers cause greater microvascular occlusion as compared to healthy cells. This links the polymer burden directly with rigidness of RBCs and vaso-occlusive risk (Sekyonda et al., 2025).

Genetic modifiers of disease severity

High levels of fetal hemoglobin (HbF) are associated with lower disease severity and death chances that makes it an important disease modifier. HbF is

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typically expressed during fetal development and begins to decrease as adult hemoglobin takes its place. Instead of the two beta-globin molecules that are present in adult hemoglobin, HbF is a tetrameric molecule made up of two alpha-globin and two gamma-globin molecules (De Souza et al., 2023; Sharma et al., 2023).

HbF persistence in adults with SCD provides clinical benefits to patients. Current available therapies like hydroxyurea, chronic blood transfusion and selected use of selective allogeneic hematopoietic stem cell transplantations have significantly reduced complications and improved survival in selected patients (Frangoul et al., 2022; Rotin et al., 2023; Sharma et al., 2023).

But HSC is way limited because of immunological challenges and shortage of well-matched donors. More recent research reveals the possibility of gene therapy, using modified hematopoietic stem cells with recently developed treatments that provide notable advantages, such as CASGEVY, LYFGENIA, and ZYNTEGLO (Kabrah, 2025).

A change from γ-globin to β-globin gene expression signifies the transition from fetal hemoglobin (HbF) to adult hemoglobin (HbA), initiating shortly after birth. HbA becomes the predominant form by approximately six months of age while HbF level remains low in adults (Desai et al., 2024). Hereditary persistence of HbF (fetal hemoglobin) HPFH results, as some people has the capacity to manufacture residual HbF. This capacity leads to milder clinical phenotypes in SCD (De Souza et al., 2023; Sharma et al., 2023).

Genetic variations in the γ-globin promoter, as well as regulatory regions such as BCL11A and the HBS1L-MYB intergenic region (Frangoul et al., 2024), that are linked with increased γ-globin expression and HPFH phenotype, have been shown to give potential benefits for patients that have sickle cell disease (SCD) (Grimley et al., 2021).

When compared to conventional treatments, the promise of gene-based therapies specifically, CRISPR-Cas9 genome editing and lentivirus-based gene addition, represents greater efficacy in reducing vaso-occlusive crises (VOCs), the acute chest syndrome (ACS), and also transfusion dependence (Frati et al., 2024).

Early clinical data indicate their role in stroke prevention, with patients maintaining a stroke-free status and often discontinuing previous chronic transfusions. This suggests gene therapy may provide lasting cerebral protection without the immunologic risks of donor transplantation. Recent findings show that while specific polymorphisms can enhance HbF in hydroxyurea-treated SCD patients, their relationship with SCD complications were not conclusively linked to HbF levels (Allard et al., 2022; Li & Mandal, 2024).

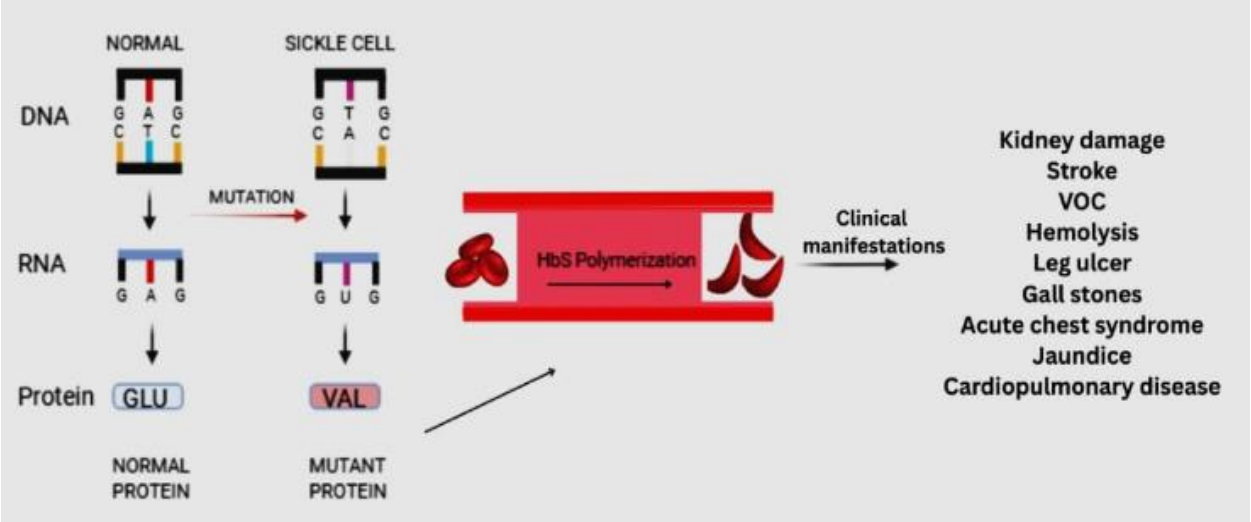

Fig.01: Molecular defect and pathological effects in sickle cell disease.

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Pathophysiology

The most widespread, well-known manifestation of sickle cell disease (SCD) is (VOC) vaso-occlusive crisis, which can cause a number of other clinical issues, such as oxidative stress, hemolysis, anemia, inflammation, and vasculopathy (Ofori-Acquah, 2020).

In addition to causing inflammation and distal tissue ischemia, the VOC has been linked to severe painful crises in SCD patients. In SCD, HbS polymerizes rapidly under deoxygenation. This process is initially reversible but becomes more persistent with repeated cycles. Hemolytic anemia and vaso-occlusion are caused by HbS polymerization, which deforms the red blood cells by making the rigid fibers (Williams & Wood, 2023).

This affects blood flow in small capillaries and some large arteries. The shorten lifespan of erythrocytes in SCD, results in hemolysis and persistent hemolytic anemia. Red blood cell sickling in tissues and unsickling in the lungs provide an explanation for this (Sekyonda et al., 2025). Inflammatory reactions occur due to recurrent VOC and chronic hemolysis result in vasculopathy. This can damage a number of organs, including the brain, liver, kidney, lung, spleen, and bones, both as acute and long-term complications (Onimoe & Rotz, 2020).

HbS polymers also show a variety of cellular abnormalities that are part of the general pathophysiological mechanisms of sickle cell disease. Avascular necrosis, chronic anemia, cerebral infarction, leg ulcers, retinopathy, and damage or failure of a variety of organs (Metaferia et al., 2022), including the heart, kidney, lung, and liver, are among the chronic consequences associated with sickle cell disease (SCD) (Abbasi, 2021).

Acute anemia, acute chest syndrome, cholecystitis, hepatic crisis, multisystem organ failure, discomfort, priapism, stroke, and splenic sequestration are examples of immediate consequences (Abbasi, 2021). Chronic issues are currently the main cause of death for older SCD age groups due to these related clinical symptoms (Abboud, 2020).

Clinical manifestations

Chronic anemia

One of the complications of SCD is chronic anemia because sickled RBCs are prone to hemolysis and have shorter life span. This leads to fatigue, breathing difficulties and poor carrying capacity for oxygen (Khan et al., 2022).

Hyper-hemolysis

It is sometimes overlooked syndrome that occurs as an uncommon consequence of repeated blood transfusions. It has quick development and resemblance to other SCD consequences (Kalter et al., 2021)

The incidence of HHS in SCD has not yet been well established in the literature. As hemoglobin levels are low in SCD patients, both native and donor RBCs undergo further hemolysis and results in more decreased post-transfusion hemoglobin levels, due to subsequent blood transfusions. It may express acutely after seven days of transfusion or may take longer during which alloantibodies are more likely to develop (Shankar et al., 2021).

Stroke

Stroke is another complication that occurs due to SCD. Sickled RBCs may block the cerebral arteries (vaso-occlusion) that provide oxygen to brain. Any disruption in oxygen and blood supply to brain may result in severe brain injury (Abbasi, 2021). Patients with sickle cell anemia are more likely to suffer a second or third stroke. It is common in children, with ischemic stroke affecting a significant proportion of patients by early adulthood (Kirkham & Lagunju, 2021).

Jaundice

Chronic hemolysis causes sickled red blood cells to degrade quickly, releasing bilirubin more quickly than the liver can eliminate it. Jaundice is the result of bilirubin building up in the body (Idris et al., 2022). Gallstones and eventually cholecystitis could result from this elevated bilirubin levels (Taher et al., 2025).

Priapism

Priapism is the name for a persistent, often painful erection that can occur with or without sexual stimulation. It is caused by sickled cells blocking penile blood flow, and if therapy is postponed, it may result in erectile dysfunction. Ischemic priapism is the most prevalent symptom in children and adults

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with sickle cell disease (SCD), occurring at least once in about 33% of adolescents and adults (Idris et al., 2022).

Acute and chronic pain

As they get older, 30–40% of SCD-affected teenagers and adults experience chronic daily pain as it worsens with age. Vaso-occlusion of sickled red blood cells with ischemia-reperfusion injury (Williams & Wood, 2023) and tissue infarction in one or more specific anatomical locations, such the arm, leg, or back, is significantly linked to acute pain. The sensitivity of the central and/or peripheral nerve systems can lead to chronic pain, which often diffuses with neuropathic pain features (Sharma & Brandow, 2020).

Vaso-occlusion

Usually, the precipitating cause of VOCs is unknown. But due to deoxygenated and rigid HbS, the most likely physiological trigger of vaso-occlusion is hypoxemia. This may occur due to respiratory complications or acute chest syndrome, dehydration (hemoconcentration is also a common mechanism) and changes in body temperature. Lowered body temperature may result in emergency crises due to peripheral vaso-constriction (Holdford et al., 2021).

Splenic sequestration

It is a life-threatening emergency situation in SCD where sickled RBCs get stuck in spleen, causing pooling of blood in liver ultimately leading to swelling. Trapped RBCs reduce circulating blood count that leads to severe anemia and hypovolemic shock (Ladu et al., 2021).

Diagnosis of SCD

Sickle cell disease's timely and accurate diagnosis is very crucial as it provides prevention of disease severity. The diagnosis of SCD depends on the combination of population based on molecular and biochemical strategies. It also includes the detection of hemoglobin variants detection, new born screening program and mutation analysis (Kazadi et al., 2024). These methods help to differentiate the carrier and the disease states and ensures the early therapeutic interventions. It also provides genetic counseling for families affected by Hemoglobinopathies (Brandow & Liem, 2022; Hassan et al., 2024).

Hemoglobin electrophoresis

Hemoglobin electrophoresis is a basic and widely used technique. This technique helps to separate different types of hemoglobin based on their electric charges. This test helps to detect whether the person has HbA, HbS or not or some non-ordinary type of HB. This technique is especially used to detect the carriers and is also used to diagnose the disease. It also helps to identify if the patient is homozygous (HbSS) or heterozygous (HbAS) carrier (Brandow & Liem, 2022).

High performance liquid chromatography (HPLC)

HPLC is more advanced and sensitive technique. It is used to measure the Hb quantity in blood and also the Hb variants. It provides the HbA, HbS, HbA^{2}and HbF fractions and also differentiate between the carrier and the affected individuals. HPLC is especially used in newborn screening as it helps in early diagnosis and in early clinical management and provides the accurate precision. (Brandow & Liem, 2022; Kazadi et al., 2024).

Molecular diagnosis: PCR and DNA sequencing

This method diagnosis the disease on gene level. In this method HBB gene sequence is observed to identify of Glu6Val mutation is present or not. If mutation occurs it will cause disease. Molecular Diagnosis is used when Electrophoresis or HPLC give unclear consequences. This method helps to detect the carrier status and also provide genetic counseling of people (Brandow & Liem, 2022). Molecular Diagnosis is useful for prenatal testing and also provides the most accurate identification of the affected fetuses. It also enables better planning for preventive measures (Hassan et al., 2024).

Newborn screening programs

In this screening program newborns blood is collected right after the birth whether the baby is of highly risked family or normal population. Blood sample use to detect the abnormal pattern of HB using HPLC or Electrophoresis methods (Rico-Mendoza et al., 2025).

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Early detection through screening enables to use preventives like Vaccination, penicillin also provide educational awareness for family about SCD. This method has shown the improved results and also reduce the chance of SCD in infants (Brandow & Liem, 2022).

Current therapeutic approaches

Managing sickle cell disease (SCD) has evolved over last few years. It is widely used treatment focusing on both relief from symptoms and modifying the disease. Current treatment strategies include medications, blood transfusions, hematopoietic stem cell transplants, and supportive care measures, like pain management. These techniques seek to avoid organ damage, reduce vaso-occlusive crises (VOC), and enhance SCD patients' general quality of life (Brandow & Liem, 2022).

New and emerging treatments (2020–2025)

Hydroxyurea therapy

Hydroxy urea is the most effective and widely used treatment for SCD. By raising the amount of fetal hemoglobin HbF, it lessens the sickling of red blood cells. Consequently, it lessens the degree and intensity of vaso-occlusive crises. Long-term use of hydroxy urea reduces the requirement for blood transfusions and hospital stays (Rico-Mendoza et al., 2025).

Blood transfusion therapy

In this treatment patients are provided with the healthy blood to reduce the number of HbS and for RBCs to flow in blood more efficiently. Blood transfusion therapy prevents from stroke, acute anemia and acute chest syndrome. Donor can face few challenges, it can cause iron overload (due to more blood donating), Alloimmunization which is an immune response or can cause transfusion reactions (Brandow & Liem, 2022).

Hematopoietic stem cell transplantation

This is the only curative therapy which is possible for few patients. In HSCT patient's stem cells are replaced with the donors for the production of healthy RBCs. This treatment is age and donor availability dependent. HSCT also face some limitations like, suitable donor is not available for every patient, high risk of Graft-versus-host diseases and many other complications (Yassin et al., 2025).

Pain management

Pain crisis is the biggest challenge in SCD patients. Pain management treatment includes NSAIDs and opioids (pain relief medicine), IV fluids, Individualized hospital protocols. These steps help to reduce the hospital admission needs and acute pain (Brandow & Liem, 2022).

Emerging gene therapy

Recently significant advancement in the development of curative and disease modifying therapies of sickle cell disease (SCD) has been seen. Particularly concentrating on the gene therapy, gene editing and pharmacological approaches. These emerging strategies aim to correct the genetic defects or to reduce pathological results such as vaso-occlusion and hemolysis (Rico-Mendoza et al., 2025).

Gene therapy strategies

Gene therapy modifies the hematopoietic stem cells of the patient by fixing the gene. A functioning β-globin gene or an anti-sickling hemoglobin variation is introduced into hematopoietic stem cells by lentiviral therapy. It allows the long-term production of RBCs (Frati et al., 2024). CRISPR-Case9 directly corrects the Glu6Val mutation in HBB gene or reactivate the fetal hemoglobin to inhibit sickling. These therapies give promising results: some patients achieve near normal hemoglobin level (Brandow & Liem, 2022; Rico-Mendoza et al., 2025; Yassin et al., 2025).

Emerging pharmacologic therapies

Recently, few new medicines play the crucial role in SCD treatment, voxelotor prevents the polymerization of HbS and reduces the hemolysis of RBCs. Crizanlizumab P-selectin inhibitor, inhibits the RBCs adhesion in blood vessels and reduces the number of VOC. L-glutamine reduces the oxidative stress and lessens the chronic complications (Herity et al., 2021). Both modern medications and traditional treatments have lessened the intensity of the illness and improved the patients' quality of life (Rico-Mendoza et al., 2025; Yassin et al., 2025).

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Future directions and clinical trials

SCD future research focusing on the next generation editing technology on advanced gene editing techniques, includes base editors and prime editing which are safer and more precise. It includes the development of Anti adhesion therapies, and Anti-inflammatory agents to prevent RBCs sticking to the blood vessels and reduce the inflammation. It also focusing on personalized treatment plans which are according to the patient's genetic profile. Also, the main aim is to provide cost effective and accessible curative therapies so that every patient can get treatment (Herity et al., 2021; Rico-Mendoza et al., 2025).

Complications and prevention strategies for SCD carrier couples

Complications in reproduction and pregnancy

Male with sickle cell disease may face problems such as reduced sperm count and dysfunction. Their sexual health or quality of life may be affected due to experiences of priapism (Idris et al., 2022). In men hypogonadism occurs due to improper functioning of the testes. Because of this, the testes produce a low level of testosterone or an insufficient amount of sperm (Idris et al., 2022; Malinowski et al., 2021).

In females carrying a pregnancy with Sickle cell disease, there.is an increase the risk of premature birth of baby, high blood pressure, death of the mother and other complications (Malinowski et al., 2021).

With the disease of Sickle cell disease carrying the pregnancy in women is highly risky it causes numerous complications for mother and fetus. Vaso-occlusive crisis (painful episodes) is a common complication for mother that cause dehydration low oxygen level stress during the pregencey.50% women during the pregnancy may face the severe painful episode. In condition of Severity of pain crisis, they may require hospitalization (Ballas & Darbari, 2020). Women with SCD face complication of anemia. It is exacerbated by increased demand of oxygen or iron during the pregnancy. Management of anemia is challenging during pregnancy especially, when safe blood is available limited (E. I. Obeagu & Obeagu, 2024).

Psychological issues

SCD not only causes the physical pain or problems. However, it also causes psychological and emotional stress. Red blood cell deformation into a sickle shape. This deformity results in blood artery blockage, which can lead to organ damage, chest discomfort, and stroke. Patient is stressed due to emotionally or physical complications (E. I., & O. G. U. (2024). Obeagu, 2024; E. I. Obeagu et al., 2023; E. I. Obeagu & Obeagu, 2024).

Patients experience physical stress as a result of pain and crisis management, which impacts their everyday activities and quality of life. Effective pain management requires a thorough understanding of the nature of physical stress (Smith et al., 2023). Patients with sickle cell disease experience stress because their pain is unpredictable and prolonged (E. I. Obeagu & Obeagu, 2024).

When patients with SCD is emotionally depressed they may fail to adhere treatment routine, reduce their willingness. They don't take part in any activities, miss medical appointments. The patient's quality of life and relationships are impacted by these emotional elements, which may also have an effect on the patient's health or frequency of pain crises. In addition to having an impact on physical health, sickle cell anemia can also induce emotional or psychological stress or organ damage. Counselling or pain management can support to improvement of quality of life in patients (Al-Marzouki et al., 2021).

Vaccination strategies

Vaccination strategy get attention due to their significant role in protection process in SCD patients from infection (Ochocinski et al., 2020). These infections are caused by pneumococcus, Hemophilus influenza, and meningococcus. Aim of these vaccines reduce the incidence of infection. Work on formation of new vaccine or boost shot has started. Aim of this new research provides the better protection to patients from the SCD. All boosted new vaccine types are tested to help the body to boost the immune system. Research area in SCA treatment is combination therapy to address the simultaneously different aspect of disease (Alzomor et al., 2022).

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Education strategies

Fundamental aspect of education and self-care strategies managing sickle cell anemia and empowering the individual with knowledge how to control their health with usage of skill (Prince et al., 2024). Education of patients provide help to understand nature of disease and its control. Education contains some other topics like medication strategies, how to managing pain etc. Education and self-care skill is very important for patients to manage their basis routine. Education involves teaching the patient about different forms of disease, how to manage disease. Education enables the patient to make pain management plan or seek medication when it is necessary. Techniques like breath exercises, relaxation, help the patients cope with pain (E. I. Obeagu & Obeagu, 2024).

Genetic counselling and preconception carrier screening

SCD is an autosomal recessive disorder, if both parents have SCD, all their children will inherit disease. If one parent is SCD or another partner carry it trait. Approximately 50% chance of inheriting SCD trait or 50% chance inheriting SCD. Children have a 25% probability of developing sickle cell disease if both parents have the trait. 25% of children will have normal hemoglobin, and 50% will be carriers. Determination of the genotype of the individual who will carry in pregnancy are advised to both partners. It also provides help in determination the presence of disorders of hemoglobin in their partners (Aggarwal & Bhat, 2023).

Through this preconception counselling or screening identifies couple who may have a high risk of SCD inherited children before the pregnancy. If risk is high counsellor recommend couple to exploring option of pre implications during vitro fertilization. In which option first of fall testing embryo and then selecting one without the disease for implantation. It is not suitable for everyone due to its high cost or invasive in nature. If risk is identified consultant enables early genetic tests like chorionic villus sampling or amniocentesis (Edwards & Laing, 2022).

Conclusion

Globally, sickle cell disease continues to be a complicated, multi-system genetic disorder with significant clinical, social, and economic ramifications, especially in areas with limited resources. Understanding of its molecular mechanisms, such as hemoglobin S polymerization, red blood cell pathomechanics, and the function of genetic modifiers like fetal hemoglobin, has greatly improved over the last ten years. Better diagnostic techniques, early detection through newborn screening, and more potent disease-modifying treatments have all resulted from these discoveries.

Emerging pharmacologic agents and gene-based therapies have changed the therapeutic landscape and provide realistic prospects for long-term disease control and functional cure in certain patients, while traditional treatments like hydroxyurea and transfusion therapy continue to lower morbidity and mortality. Accessibility, cost, long-term safety, and equitable implementation are still issues, though. In order to maximize results, future initiatives must concentrate on increasing access to cutting-edge treatments worldwide, bolstering preventive measures through genetic counselling and education, and incorporating individualized strategies. To direct future research and enhance the quality of life for sickle cell disease patients worldwide, a thorough understanding of the disease's mechanisms, symptoms, and management is crucial.

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