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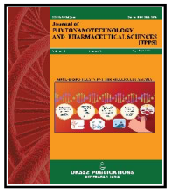

Review Article : Open Access

Emerging therapies and management approaches in sickle cell disease (SCD): A critical review

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Abstract

This comprehensive review delves into the intricate landscape of sickle cell disease (SCD), a global genetic disorder impacting individuals, healthcare systems, and communities. The article traces the historical origins of SCD, providing an in-depth exploration of its complex pathophysiology and the myriad clinical complications it engenders. Traditional management approaches, including pain management, blood transfusions, and hydroxyurea therapy, are scrutinized alongside assessing their associated limitations and challenges. Innovative therapies on the horizon, such as gene therapy, CRISPR/Cas9-based gene editing, and strategies to induce fetal hemoglobin production, offer glimmers of hope for potential curative interventions. Patient perspectives are seamlessly integrated, offering invaluable insights into the daily challenges and lived experiences of individuals grappling with SCD. The review underscores the pivotal role of multidisciplinary care teams, preventive strategies, patient education, and psychosocial support in optimizing SCD care. Furthermore, it examines the influence of healthcare policies, research funding, and advocacy organizations in propelling advancements in SCD management. Peering into the future, the article discusses the prospects of curative breakthroughs, precision medicine, enhanced pain management, and improved quality of life for SCD patients. It underscores the imperative of sustained research, collaborative efforts, and advocacy initiatives to tackle disparities, ensure equitable access to care, and foster innovation in SCD management.

This comprehensive review provides a panoramic view of SCD, accentuating its complexities and the potential for transformative change in the lives of those affected. It issues a resounding call to action, championing continuous endeavors to enhance SCD care and pave the way for a brighter, healthier future for all impacted individuals.

1. Introduction

Sickle cell disease (SCD), a hereditary hemoglobinopathy, is a paradigm of genetic complexity and clinical diversity. First described over a century ago, this genetic disorder has been the focus of extensive research and clinical efforts. It is characterized by a single point mutation in the β-globin gene that produces abnormal hemoglobin S (HbS) molecules, causing red blood cells to take on a characteristic crescent or "sickle" shape when deoxygenated. This seemingly subtle alteration in hemoglobin structure triggers a cascade of pathophysiological events, resulting in many clinical complications (Conran *et al*., 2018; Mc Cormick *et al*., 2021).

The clinical manifestations of SCD are broad and often debilitating, encompassing recurrent vaso-occlusive crises, hemolytic anemia, organ damage, and a shortened lifespan. These complications substantially burden affected individuals and significantly strain healthcare systems worldwide (Frenette *et al*., 2007). Sickle cell disease affects millions globally, mostly in sub-Saharan Africa, India, and the Middle East. Moreover, due to migration and globalization, SCD is increasingly recognized as a global health issue, affecting populations in North America, Europe, and other regions. The staggering prevalence of SCD, its chronic nature, and associated healthcare costs underscore the urgent need for innovative and effective therapeutic approaches (Conran and Johan, 2018; McCormick *et al*., 2021). The purpose of this review article is to examine the emerging therapies and management approaches in the field of sickle cell disease. By synthesizing current research findings, ongoing clinical trials, and patient perspectives, we aim to provide a comprehensive overview of the evolving landscape of SCD care. This review will explore the latest developments in treatment modalities, including gene therapies, gene editing techniques, and novel pharmaceutical agents, while also considering the broader strategies for disease management. Additionally, we will highlight the challenges and opportunities in the field and emphasize the importance of collaborative efforts to improve the lives of individuals living with SCD (Shah *et al*., 2018).

This article focuses on the molecular underpinnings of SCD, explores traditional management strategies, and critically assesses the potential

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of emerging therapies. Also, consider the holistic approach to SCD care, encompassing psychosocial support, patient education, and healthcare policy. Ultimately, our review aims to provide insights contributing to the ongoing pursuit of effective treatments and improved quality of life for SCD patients.

2. Historical perspective

Sickle cell disease (SCD) occupies a unique place in the annals of medicine, marked by a rich history of discovery and scientific progress. Its story begins with the realization that an unassuming genetic mutation could give rise to a complex and debilitating disorder.

2.1 Early observations and discovery

The first recorded observation of SCD-like symptoms dates to the early 20th century, but the condition was not widely recognized until the landmark work of Dr. James B. Herrick in 1910. Dr. Herrick, a Chicago-based physician, reported a puzzling case of anemia in a dental student of African descent. His astute clinical observation of abnormal red blood cell shapes in a blood smear led to the term "sickle-shaped cells." This seminal case report marked the birth of our understanding of SCD (Power-Hays *et al*., 2020).

2.2 The role of hemoglobin S

It was not until the 1940s that the underlying genetic basis of SCD was elucidated. In groundbreaking research, Dr. Linus Pauling and his colleagues identified that SCD was linked to an abnormal form of hemoglobin, which they named hemoglobin S(HbS). This discovery laid the foundation for subsequent genetic investigations and opened the door to developing diagnostic tests for SCD (Conran *et al*., 2020; Mangano *et al*. 2015; Power-Hays *et al*., 2020).

2.3 Clinical advances and complications

Throughout the mid-20th century, clinical researchers and physicians gradually unraveled the clinical complexities of SCD. They identified vaso-occlusive crises, hemolytic anemia, and complications in multiple organ systems as key disease features. The recognition of these clinical manifestations highlighted the need for improved treatments and management strategies (Salinas Cisneros *et al*., 2020).

2.4 Pioneering treatments and hydroxyurea

Historically, SCD was fraught with high mortality rates in childhood. However, advancements in healthcare, particularly the widespread use of penicillin prophylaxis and vaccines in the mid-20th century, significantly reduced early mortality. It was not until the late 20th century that hydroxyurea, a medication that increases fetal hemoglobin levels and reduces sickling, emerged as a transformative therapy for SCD (Cokic *et al*., 2003).

2.5 The genomic era and beyond

The advent of the genomic era brought unprecedented insights into the molecular basis of SCD. The discovery of additional hemoglobin variants genetic modifiers, and the elucidation of the complex pathways leading to vaso-occlusive crises marked a turning point in our understanding of the disease. Moreover, the 21st century witnessed remarkable progress in gene therapy and gene editing techniques, opening new possibilities for the treatment and potential cure of SCD (Frenette *et al*., 2007). In this historical perspective section, we have traced the trajectory of our understanding of SCD from its early recognition as a clinical entity to the contemporary era of advanced therapies and genetic insights. This historical backdrop sets the stage for a critical examination of the emerging therapies and management approaches in the subsequent sections of this review article.

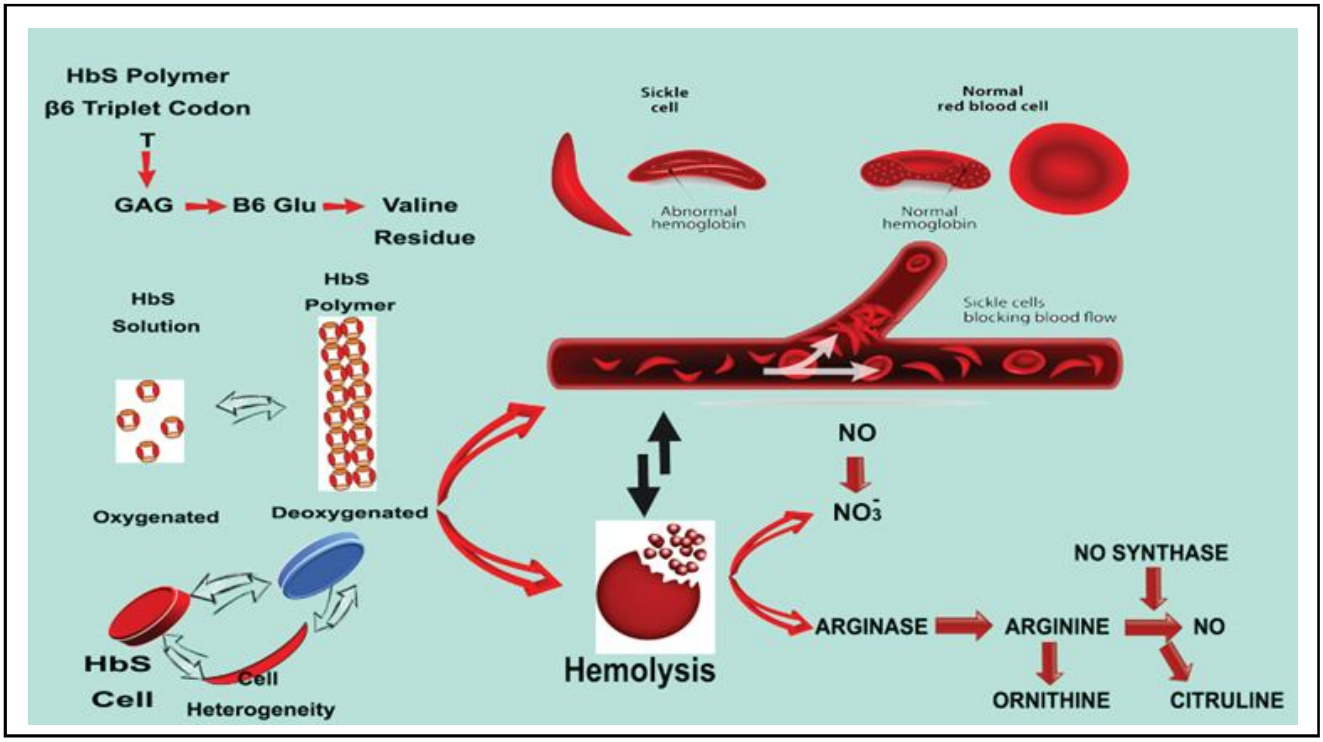

Figure 1: The pathophysiology of sickle cell disease involves a mutation in hemoglobin known as HbS or HBB glu6val.

3. Pathophysiology (Martin H. Steinberg 2008; Sundd, Gladwin *et al.*, 2019)

Sickle cell disease (SCD) is characterized by a complex interplay of molecular, cellular, and physiological changes that result from a single genetic mutation. Understanding the pathophysiology of SCD is crucial for appreciating its clinical manifestations and the rationale behind emerging therapies. The pathophysiology of sickle cell disease involves a mutation in hemoglobin known as HbS or HBB glu6val. This mutation results in the production of β-globin chains that, when combined with normal β-globin chains to form hemoglobin tetramers, give rise to hemoglobin HbS. HbS can undergo reversible polymerization when it is deoxygenated, leading to the formation of sickle-shaped cells. These sickle cells cause damage to the erythrocyte membrane, eventually leading to irreversible membrane damage. Furthermore, these abnormal cells have a shortened lifespan due to hemolysis, some of which occurs within blood vessels, depleting nitric oxide (NO). Sickle erythrocytes are also responsible for vas occlusion, further contributing to the pathophysiology of the disease (Sundd, Gladwin *et al*., 2019).

3.1 Molecular mechanisms: Hemoglobin S (HbS)

The cornerstone of SCD pathophysiology lies in the genetic mutation affecting hemoglobin, the oxygen-carrying protein in red blood cells (RBCs). In SCD, a point mutation in the β-globin gene produces abnormal hemoglobin called hemoglobin S (HbS) (Salinas Cisneros *et al*., 2020; Schaer *et al*., 2013; Sundd *et al*., 2019). Following points to important for mechanism understanding.

- **HbS polymerization:** HbS tends to polymerize, especially under low oxygen conditions, causing RBCs to deform into a characteristic sickle shape. This leads to impaired blood flow and tissue hypoxia.
- **Sickling cascade:** The polymerization of HbS triggers a cascade of events, including membrane damage, decreased RBC deformability, and increased adhesion to endothelial cells.
- **Hemolysis:** Sickle RBCs are fragile and prone to hemolysis, contributing to anemia in SCD.

3.2 Cellular mechanisms: Sickling of red blood cells

The sickling of RBCs is a hallmark feature of SCD and plays a central role in the pathophysiology. Sickle cell disease (SCD) is a genetic disorder characterized by the presence of abnormal hemoglobin (HbS) in red blood cells (RBCs), which can lead to various complications. The sickling of RBCs is a central feature of SCD and is primarily caused by deoxygenation-induced changes in these cells (Schaer *et al*., 2013). Here is an explanation of the key points you mentioned:

3.2.1 Deoxygenation induced sickling

In individuals with SCD, hemoglobin S (HbS) is abnormal because of a genetic mutation. When HbS loses oxygen molecules, it undergoes a structural change. In the oxygenated state, HbS behaves similarly to normal hemoglobin (HbA) and remains soluble within the RBCs.

Deoxygenation occurs in the venous circulation as RBCs transport oxygen from the lungs to the tissues. When HbS loses its oxygen, it forms long, rigid polymers inside the RBCs. These polymers cause the usually flexible, biconcave-shaped RBCs to distort and take on a characteristic sickle shape. The sickle-shaped RBCs are less flexible and more prone to clumping together, making them less efficient at transporting oxygen. Additionally, their altered shape can damage the RBC membrane and a shorter lifespan than normal RBCs (Kato *et al*., 2018; Wang *et al*., 2021).

3.2.2 Obstruction of blood vessels

The sickle-shaped RBCs tend to adhere to one another due to the sticky nature of the HbS polymers. This tendency to clump together is exacerbated when RBCs lose oxygen and sickle. In small blood vessels, such as capillaries, the sickle-shaped RBCs can become lodged or stuck, obstructing blood flow. This can lead to vaso-occlusive crises, which are painful episodes of tissue ischemia (lack of blood flow) caused by the blockage of these small vessels. Vaso-occlusion can occur in various organs and tissues, leading to multiple symptoms and complications, including severe pain, organ damage, and stroke (Kato *et al*., 2018).

3.2.3 Tissue hypoxia

When blood flow is obstructed by sickle-shaped RBCs, the tissues downstream of the blockage are deprived of oxygen, leading to tissue ischemia. This lack of oxygen in the affected tissues is known as tissue hypoxia. Tissue hypoxia can cause severe pain, a hallmark feature of SCD, and is often referred to as a vaso-occlusive crisis or pain crisis. The pain can be excruciating and can be localized to specific areas of the body, such as the chest, joints, abdomen, or bones. Prolonged or recurrent episodes of tissue ischemia and hypoxia can also damage organs and tissues, contributing to the chronic complications seen in SCD, such as organ failure, stroke, and chronic pain (Kato *et al*., 2018).

In summary, the sickling of RBCs in SCD is primarily triggered by deoxygenation, leading to the formation of rigid, sickle-shaped cells. These abnormal cells can clump together and block small blood vessels, causing vaso-occlusive crises and tissue hypoxia, responsible for the characteristic pain and complications associated with the disease.

3.3 Clinical complications

The pathophysiological changes in SCD give rise to a wide range of clinical complications that significantly impact patients' lives. Following difficulties were address.

- **Vaso-occlusive crises:** Explain how vaso-occlusive crises occur due to the blockage of blood vessels by sickle-shaped RBCs, leading to acute pain and potential organ damage.
- **Hemolytic anemia:** Discuss the chronic hemolysis of sickle RBCs, which results in anemia, jaundice, and fatigue.

3.3.1 Organ damage

Describe how SCD can lead to cumulative organ damage over time, affecting the spleen, liver, lungs, brain, kidneys, and bones. Highlight the chronic nature of these complications and their impact on quality of life.

In this section, you have provided a detailed overview of the molecular and cellular mechanisms underlying SCD, focusing on the role of hemoglobin S and the sickling of red blood cells. Additionally, you've discussed the various clinical complications associated with SCD, emphasizing the diverse and profound effects of the disease on affected individuals. This understanding forms the basis for exploring emerging therapies and management approaches in the subsequent sections of your review article.

4. Conventional management approaches (Fernandes 2017; Ndefo *et al.*, 2008; Martin H. Steinberg, 2008)

The management of sickle cell disease (SCD) has historically relied on a set of conventional approaches to alleviate symptoms, prevent complications, and improve patients' quality of life. While these approaches have provided significant benefits, they are not without limitations and challenges (Frenette *et al*., 2007).

4.1 Pain management

Pain is a hallmark feature of SCD, often resulting from vaso-occlusive crises and chronic inflammation. Describe the traditional methods of pain management:

Analgesics: Discuss using non-opioid and opioid analgesics for pain relief during crises.

Non-pharmacological interventions: Mention complementary therapies such as heat, massage, and relaxation techniques.

4.2 Blood transfusions

Blood transfusions increase hemoglobin levels and improve oxygen-carrying capacity in SCD patients. Highlight the following points:

Chronic transfusions: Explain the use of regular transfusions to reduce the risk of stroke in pediatric patients.

Acute transfusions: Discuss the role of critical transfusions in managing acute complications and severe anemia.

4.3 Hydroxyurea therapy (Cokic *et al*., 2003)

Hydroxyurea, an oral medication, has significantly advanced SCD management. Discuss its uses and benefits.

Fetal hemoglobin induction: Describe how hydroxyurea increases fetal hemoglobin production, inhibiting sickling.

Clinical benefits: Highlight the reduction in pain episodes, acute chest syndrome, and hospitalizations seen with hydroxyurea therapy.

4.4 Limitations and challenges

While these conventional approaches have improved the lives of SCD patients, they are not without limitations and challenges.

Pain medication risks: Discuss the risks of opioid use, including addiction and side effects.

Transfusion complications: Address potential complications associated with chronic transfusions, such as iron overload and alloimmunization.

Hydroxyurea challenges: Mention that not all patients respond to hydroxyurea, and long-term safety data are still evolving.

Access and adherence: Highlight disparities in access to healthcare and medication adherence, which can affect treatment outcomes.

The traditional methods of managing sickle cell disease include pain management, blood transfusions, and hydroxyurea therapy. While these approaches have provided relief and improved outcomes for many patients, it is important to acknowledge their limitations and the challenges associated with their use. This sets the stage for exploring the promising emerging therapies and novel management strategies in the subsequent sections of your review article.

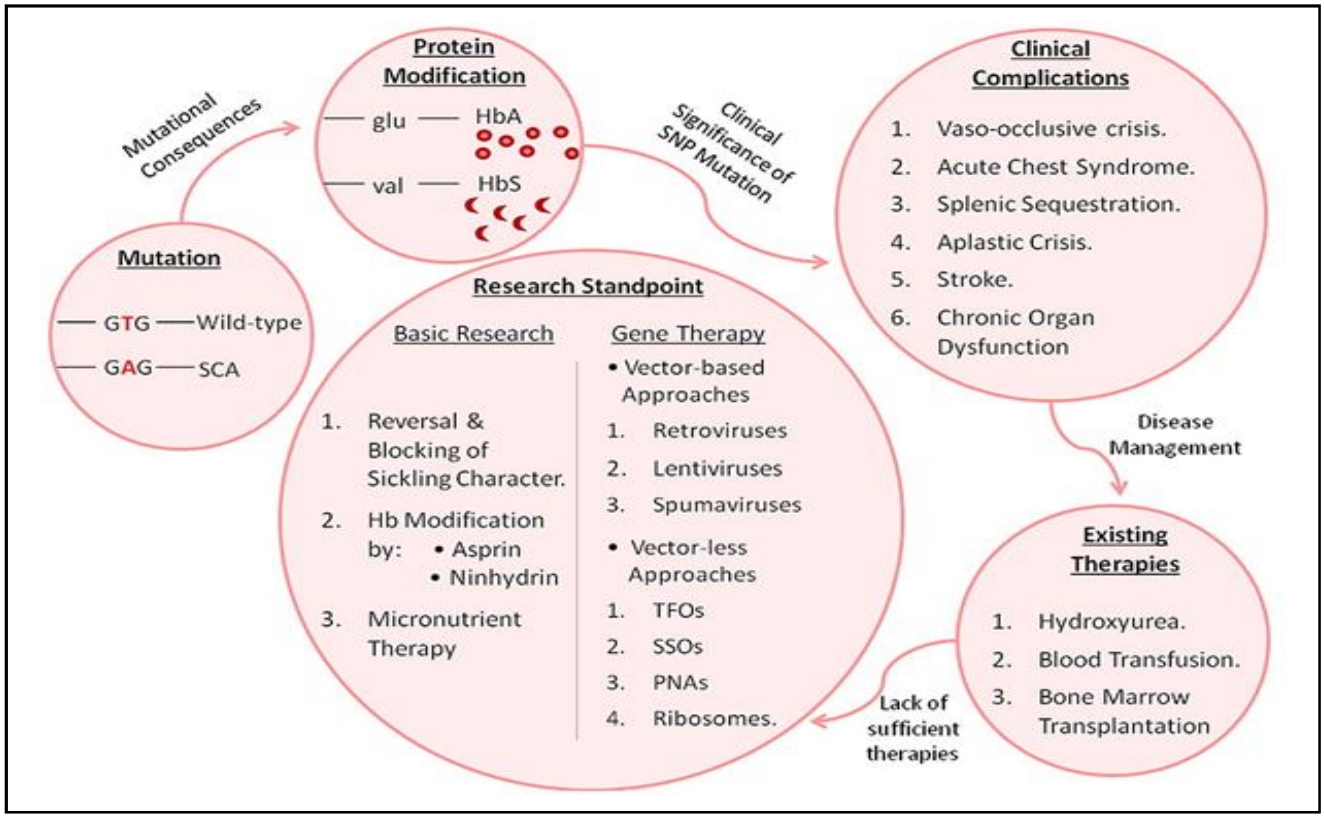

Figure 2: Treatment approaches for sickle cell anemia: A historical, current, and future perspective (Fernandes, 2017).

5. Emerging therapies (Ansari *et al.*, 2018; Nardo-Marino *et al.*, 2020; Salinas Cisneros *et al.*, 2020)

The landscape of SCD management is evolving rapidly, with promising emerging therapies offering new hope for individuals with this challenging genetic disorder. These innovative approaches aim to target the root causes of SCD and potentially provide curative solutions (Carden *et al*., 2019; Kavanagh *et al.,* 2022; Monus *et al.,* 2019).

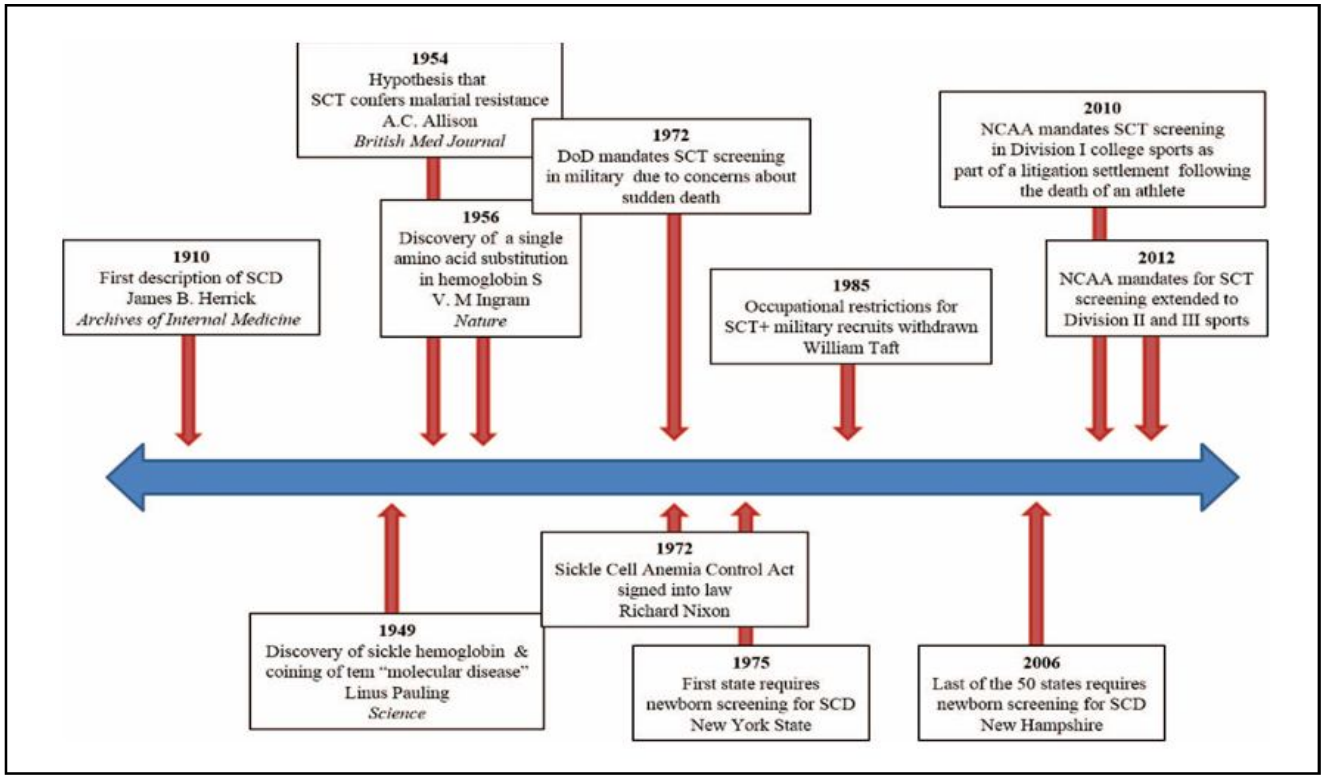

Figure 3: A chronological overview of significant events in the history of sickle cell disease diagnosis, with a particular focus on developments in the past decade (Ansari *et al*., 2018; Salinas Cisneros *et al*., 2020).

5.1 Advanced therapy

5.1.1 Hydroxyurea in sickle cell disease (SCD) management (Verma *et al*., 2018)

Hydroxyurea is a pivotal advancement in the management of sickle cell disease (SCD). This medication has proven to be a cornerstone in improving the lives of individuals affected by SCD. Hydroxyurea works by increasing the production of fetal hemoglobin (HbF), a type of hemoglobin that inhibits the abnormal sickling of red blood cells characteristic of SCD. By boosting HbF levels, hydroxyurea helps to maintain the shape and flexibility of red blood cells, reducing their tendency to form the characteristic "sickle" shape.

One of the most notable benefits of hydroxyurea is its ability to significantly reduce the frequency and severity of painful vaso-occlusive crises, which are a hallmark of SCD. This means fewer episodes of excruciating pain and reduced hospitalizations for pain management.

By reducing the burden of pain and complications associated with SCD, hydroxyurea has a transformative effect on the quality of life for many patients. It allows them to engage in daily activities more comfortably and with fewer disruptions. Hydroxyurea also contributes to minimizing organ damage and other long-term complications associated with SCD, including strokes and pulmonary hypertension. While hydroxyurea has been a game-changer in SCD management, it's essential to acknowledge that not all patients respond to the treatment similarly. Additionally, long-term safety remains a subject of ongoing research, particularly concerning potential risks of bone marrow suppression and leukemia in rare cases.

Nonetheless, hydroxyurea's positive impact on pain crisis reduction and overall well-being cannot be overstated. It has become a standard of care for many individuals with SCD and is a promising foundation for future therapeutic advancements. As researchers explore new treatment modalities, hydroxyurea remains a beacon of hope for those living with this challenging genetic disorder.

5.1.2 Transplantation as a potential cure for sickle cell disease (SCD) (Carden *et al*., 2019; Leonard *et al*., 2018)

Hematopoietic stem cell transplantation (HSCT) emerges as a beacon of hope in pursuing a cure for sickle cell disease (SCD). HSCT involves transplanting healthy hematopoietic (blood-forming) stem cells from a compatible donor, typically a matched sibling. In the case of SCD, this procedure offers the potential for a complete cure. The transplanted stem cells generate healthy red blood cells, replacing the defective ones that cause the disease. Over the years, advances in transplantation techniques and donor selection have significantly expanded HSCT's feasibility and success rates for SCD. These improvements have made transplantation more viable for a broader range of patients.

while HSCT holds immense promise, it is not without challenges. Finding a suitable matched sibling donor can be limiting, as not all patients have compatible siblings. In such cases, alternative donor sources, like unrelated donors or cord blood, are explored. The transplantation process carries risks, including graft-versus-host disease (GVHD), infections, and organ damage. These complications require careful monitoring and management.

Despite these challenges, HSCT remains a hope for individuals with SCD, particularly those with compatible sibling donors. The potential for a complete and lifelong cure is a testament to the remarkable progress in hematopoietic stem cell transplantation, offering renewed optimism for a future free from the burden of sickle cell disease.

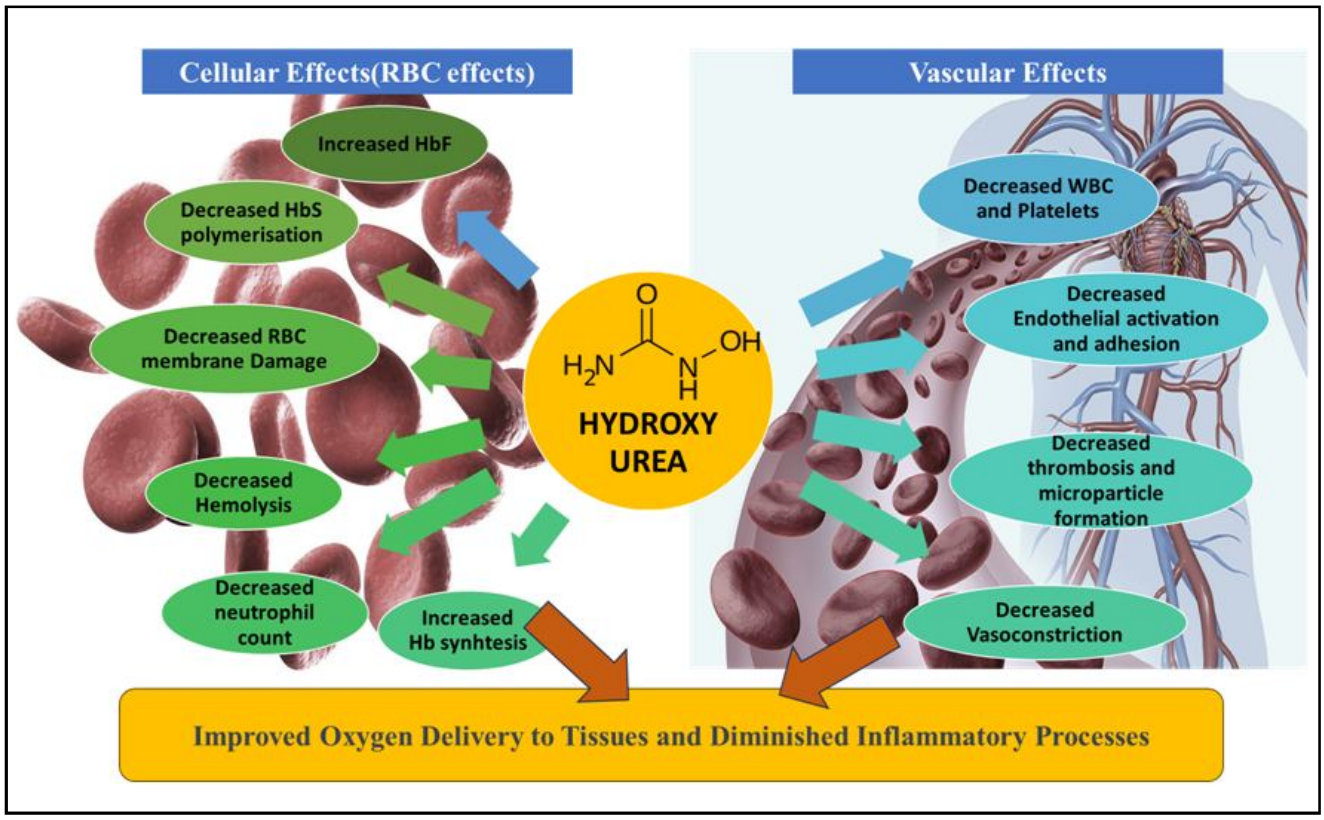

Figure 4: Various outcomes of administering hydroxyurea in individuals with sickle cell disease.

5.1.3 Gene therapy for sickle cell anemia (Kassim *et al*., 2022; Tasan *et al*., 2016)

Gene therapy is a promising field of medicine that aims to treat or prevent diseases by modifying a patient's genes. One of the areas where gene therapy has shown significant potential is in the treatment of genetic disorders, such as sickle cell disease and beta-thalassemia, which are characterized by abnormal or insufficient production of hemoglobin, the oxygen-carrying protein in red blood cells.

Gene therapy represents a groundbreaking approach to addressing the underlying genetic cause of sickle cell anemia (SCA). Gene therapy offers a promising avenue for treating SCA by addressing the root cause of the disease. It involves the introduction of a functional copy of the hemoglobin gene into the patient's cells, effectively correcting the genetic mutation responsible for SCA.

In gene therapy for SCA, a functional hemoglobin gene is inserted into the patient's bone marrow cells or hematopoietic stem cells. This corrected gene provides instructions for the production of normal hemoglobin. After the corrected gene is inserted, the patient's hematopoietic stem cells are collected. These genetically modified stem cells are then reintroduced into the patient's body. The genetically modified stem cells produce healthy, functional hemoglobin. As a result, the patient's red blood cells acquire the ability to carry oxygen without sickling, reducing the symptoms and complications associated with SCA.

Gene therapy for SCA has shown promising results in clinical trials, with some patients experiencing significant improvements in their condition. However, continued research is essential to optimize the safety and efficacy of this approach. Challenges include ensuring the long-term stability of the corrected cells and addressing potential side effects.

Gene therapy holds the potential to transform the lives of individuals with SCA by offering a curative solution. While it is still in the experimental stage, the progress made so far signifies a remarkable step toward a future where sickle cell anemia can be treated at its genetic root, offering renewed hope for those affected by this challenging genetic disorder.

Here are some strategies for inducing fetal hemoglobin production and their current development stages (Demirci *et al*., 2020; Kunz *et al*., 2020):

- **Gene editing:** Techniques like CRISPR-Cas9 are being explored to directly edit the genes responsible for regulating HbF production. Researchers are working on modifying the BCL11A gene, which normally suppresses HbF production, to reactivate HbF genes. Several clinical trials are in progress or planning stages to test the safety and efficacy of these gene-editing approaches.
- **Pharmaceutical agents:** Drugs like hydroxyurea and erythropoietin have been used to increase HbF levels in patients. While these drugs have been in clinical use for some time, ongoing research aims to develop more targeted and effective pharmaceutical agents that can elevate HbF levels without the side effects associated with current treatments.
- **Small molecules:** Small molecules, such as HbF inducers like decitabine, have shown promise in preclinical and early clinical trials. These compounds can reawaken the genes responsible for HbF production and may offer a less invasive treatment option (Stomper et al. 2019).
- **Bone marrow transplantation:** Allogeneic bone marrow transplantation, where a patient receives stem cells from a donor with a genetic predisposition for high HbF production, has shown success in curing sickle cell disease. However, this approach has limitations due to the challenges of finding compatible donors (Vermylen *et al*., 1991).
- **Genetic vectors:** Viral vectors are being investigated for delivering genes that promote HbF production into a patient's bone marrow cells. These vectors are modified to carry therapeutic genes safely. Some early-phase clinical trials have shown promise in using lentiviral vectors for this purpose (Ertl, 2022).

The development of these strategies is at various stages, with some already in clinical trials, while others are still in preclinical research. Challenges in gene therapy for increasing HbF levels include ensuring the safety and efficacy of these treatments, as well as making them widely accessible to patients. Despite these challenges, the progress in the field holds great promise for individuals with hemoglobino pathies and other genetic disorders related to hemoglobin production.

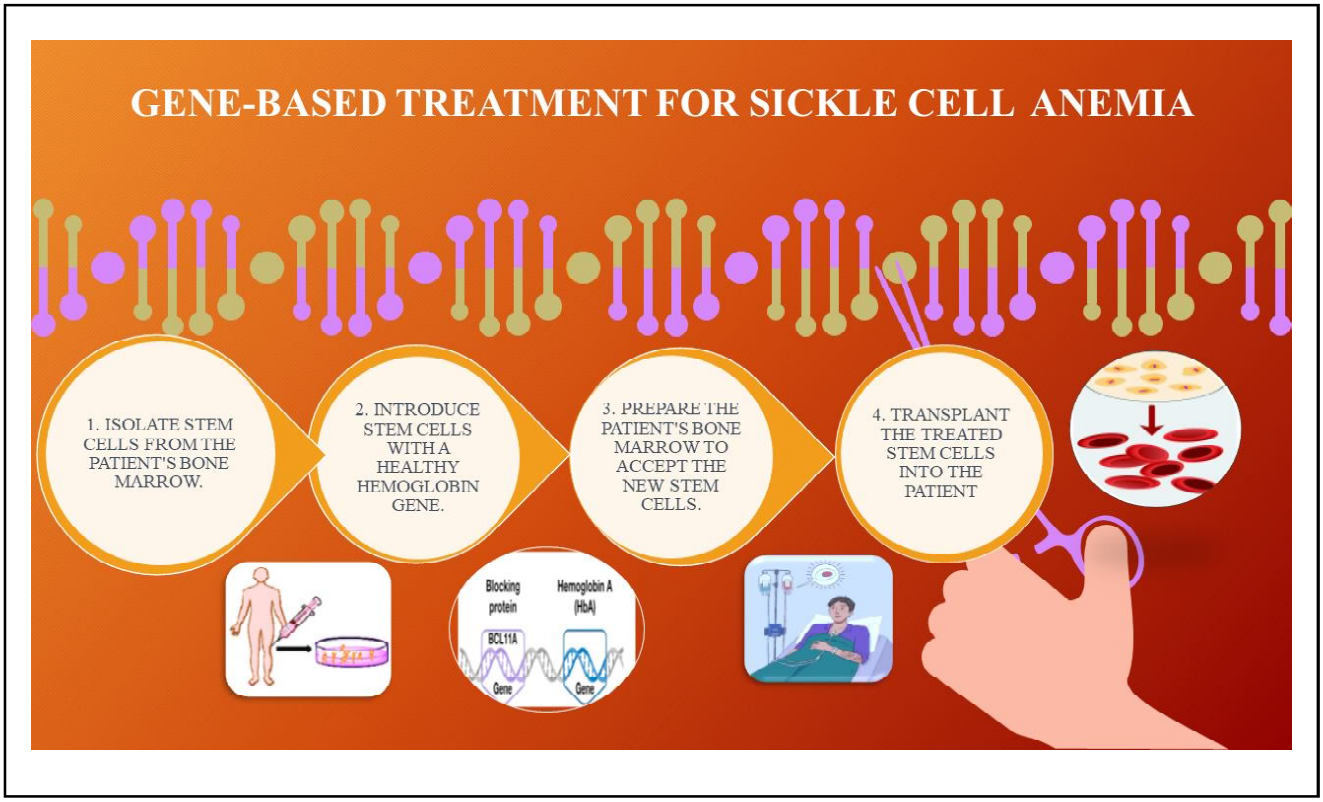

Figure 5: Sickle cell anemia and gene therapy: Mechanisms and applications.

5.1.4 Gene editing (*e.g.,* CRISPR/Cas9) for sickle cell disease (SCD) (Synthego, 2020)

Gene editing technologies, exemplified by CRISPR/Cas9, offer a transformative approach to tackling sickle cell disease (SCD) at its genetic root. This revolutionary method enables precise modifications to the patient's DNA, targeting the specific mutation responsible for SCD within the β-globin gene. By correcting this genetic anomaly, gene editing aims to restore the production of normal hemoglobin, alleviating the hallmark sickling of red blood cells. Although, gene editing for SCD is in its experimental stages, early research and clinical trials have shown promise, providing hope for a curative solution. However, rigorous safety assessments and ongoing research are necessary to address potential off-target effects and ensure this innovative approach's long-term safety and efficacy in the quest to improve the lives of individuals affected by SCD.

Focusing on strategies for inducing fetal hemoglobin (HbF) production using CRISPR/Cas9, let's delve into the current development stages (Demirci *et al.,* 2021; Finotti *et al*., 2023):

- **CRISPR/Cas9 basics:** CRISPR (clustered regularly interspaced short palindromic repeats) is a system that bacteria use to defend against viruses. Cas9 is an enzyme that acts like molecular scissors. When guided by a small RNA molecule, it can precisely cut DNA at a specific location.
- **Disrupting HbF suppression genes:** One strategy involves using CRISPR/Cas9 to disrupt genes that suppress HbF production. The BCL11A gene is a well-known repressor of HbF in adults. By editing this gene, researchers aim to reduce its activity and allow for increased HbF production. This approach is in advanced stages of development, with clinical trials underway.
- **Gene activation:** Another approach is to use CRISPR/Cas9 to activate genes responsible for HbF production. By modifying regulatory elements in the HbF genes themselves or in genes that enhance HbF expression, researchers can stimulate the production of fetal hemoglobin. This strategy is still in early stages of development and requires further research.
- **Safety concerns:** One of the critical aspects of CRISPR/Cas9-based therapy is ensuring safety. Off-target effects, where the Cas9 enzyme accidentally edits other parts of the genome, can lead to unintended consequences. Researchers are working to minimize these off-target effects through improved CRISPR/Cas9 techniques and enhanced target site selection.
- **Delivery systems:** Efficient delivery of the CRISPR/Cas9 components into the target cells, such as hematopoietic stem cells, is crucial. Various delivery methods, including viral vectors and nanoparticles, are being explored to ensure that the gene-editing tools reach the right cells in the body.
- **Clinical trials:** Several clinical trials are underway to test the safety and efficacy of CRISPR/Cas9-based gene editing for increasing HbF levels. These trials involve carefully selected patients with sickle cell disease and beta-thalassemia. Initial results have shown promise, but more data is needed to determine the long-term effects and potential complications.

In summary, CRISPR/Cas9-based gene editing holds significant promise for inducing fetal hemoglobin production as a potential treatment for hemoglobinopathies like sickle cell disease and beta-thalassemia. While some strategies are already in clinical trials, others are in earlier stages of development. Continued research, rigorous testing, and addressing safety concerns will be key in realizing the full potential of CRISPR/Cas9 in treating these genetic disorders.

5.1.5 Fetal hemoglobin induction (Stomper *et al.,* 2019)

Fetal hemoglobin (HbF) is known to effectively inhibit the sickling of red blood cells. It is a type of hemoglobin primarily produced during fetal development, gradually being replaced by adult hemoglobin (HbA) postnatally. HbF exhibits a heightened oxygen affinity compared to HbA, facilitating oxygen transfer from the maternal blood to the fetus. Notably, in sickle cell disease (SCD), a genetic disorder stemming from a mutation in the beta-globin gene resulting in the formation of abnormal hemoglobin (HbS) fibers under deoxygenated conditions, HbF plays a pivotal role in preventing the sickling of red blood cells. SCD is associated with a range of complications including pain, anemia, susceptibility to infections, organ damage, and stroke. Consequently, fetal hemoglobin (HbF) has emerged as a natural protective factor against red blood cell sickling in individuals afflicted by sickle cell disease (SCD).

Emerging therapies aim to induce HbF production in patients with SCD to reduce the severity of the disease and improve their quality of life. Some of these therapies include:

Pharmacological agents can stimulate the expression of gamma-globin genes, which encode HbF or inhibit the expression of BCL11A, a transcription factor that represses HbF. Such agents include hydroxyurea, decitabine, pomalidomide, and CRISPR-Cas9 gene editing (Martin H. Steinberg 2020).

Bone marrow transplantation or gene therapy can replace the defective hematopoietic stem cells with normal ones or correct the mutation in the beta-globin gene. These approaches can restore average hemoglobin production or increase HbF levels in the blood.

Inhibition of MRP1, a membrane protein that transports HbS out of the red blood cells and reduces intracellular HbS concentration. Blocking MRP1 can increase HbF synthesis and prevent sickling.

5.1.6 Insights into ongoing clinical trials

Indeed, here is an overview of some prominent clinical trials related to emerging therapies for sickle cell disease (SCD) as of update in September 2021.

5.1.6.1 Gene therapy trials

Bluebird bio's lentiglobin: Bluebird Bio conducted several clinical trials evaluating their gene therapy, LentiGlobin, which aims to increase healthy hemoglobin production in SCD patients (Treatment with investigational LentiGlobin™ gene therapy for sickle cell disease, bb1111). Results in complete elimination of SCD-related severe vaso-occlusive events in group C of Phase 1/2 HGB-206 clinical study presented at 62nd Annual ASH meeting - blu n.d.).

CRISPR therapeutics and vertex's CTX001: This CRISPR/Cas9-based gene-editing therapy is designed to correct the genetic mutations responsible for SCD. Clinical trials have been ongoing to assess its safety and efficacy (CRISPR Therapeutics Submits First Clinical Trial Application… | CRISPR n.d.).

5.1.6.2 HbF induction trials

BCL11A inhibition: Several trials have explored the inhibition of the BCL11A gene as a strategy to induce the production of fetal hemoglobin (HbF) in SCD patients. Increased HbF can reduce sickling (Taghavi *et al.*, 2019).

Decitabine: Clinical studies have investigated decitabine, a medication used in cancer treatment, to stimulate HbF production in SCD patients (Stomper *et al.,* 2019).

5.1.6.3 Anti-sickling agents

Voxelotor (GBT440): Voxelotor is an oral therapy that works by increasing the oxygen affinity of hemoglobin, reducing its tendency to sickle. Clinical trials have assessed its effectiveness in lowering vaso-occlusive crises (Hutchaleelaha *et al.*, 2019).

Crizanlizumab: This monoclonal antibody targets P-selectin, a molecule involved in the adhesion of sickled red blood cells. Clinical trials have explored its potential in preventing vaso-occlusive crises (Stevens *et al.,* 2021).

5.1.6.4 Other Novel Therapies

P-selectin Inhibition: Apart from crizanlizumab, other agents targeting P-selectin have been investigated in clinical trials for their potential to prevent vaso-occlusive events (Dai *et al*., 2022).

Siklos (hydroxyurea): While not new, Siklos is continually studied in clinical trials to assess its long-term safety and efficacy as a treatment for SCD.

6. Disease management strategies (Carden *et al.*, 2019; Ndefo *et al.*, 2008; Salinas Cisneros *et al.*, 2020)

Effective management of sickle cell disease (SCD) extends beyond medical interventions and encompasses a holistic approach that includes prevention, education, and psychosocial support. Multidisciplinary care teams are pivotal in providing comprehensive care to individuals with SCD (Vasava *et al.,* 2022).

6.1 Preventive measures

The importance of preventive measures in managing SCD:

- **Immunizations:** Emphasize the need for vaccinations, especially against infections like pneumococcal, to prevent serious complications.
- **Infection control:** Describe strategies to reduce the risk of infections, including prophylactic antibiotics for high-risk individuals.
- **Hydration and avoiding triggers:** Explain the significance of staying well-hydrated and avoiding known triggers of vaso-occlusive crises.

6.2 Patient education

The crucial role of patient education in empowering individuals with SCD to manage their condition:

Disease education: Discuss the importance of educating patients and their families about SCD, its complications, and the early recognition of symptoms(Chellammal. 2022).

Self-management: Encourage patients to actively participate in self-management, including monitoring symptoms and adhering to prescribed treatments.

Transition to adult care: Address the challenges of transitioning pediatric patients to adult care and the need for specialized programs.

6.3 Psychosocial support

Recognize the psychosocial aspects of SCD management:

- **Psychological impact:** Discuss the emotional and psychological challenges individuals with SCD face and the importance of mental health support.
- **Social support:** Highlight the significance of strong social support networks, including support groups and counseling services.
- **Pain management strategies:** Explore non-pharmacological pain management techniques and the role of mental health professionals in coping with chronic pain (Malik *et al.,* 2020).

6.4 Importance of multidisciplinary care teams

Acknowledge the pivotal role of multidisciplinary care teams in providing comprehensive SCD care:

- **Team composition:** Describe the critical members of a multidisciplinary care team, including hematologists, nurses, pain specialists, social workers, and psychologists.
- **Coordination of care:** Explain how these healthcare professionals collaborate to address various aspects of SCD, from medical management to psychosocial support.
- **Improving outcomes:** Highlight how coordinated care can lead to better outcomes, improved quality of life, and reduced hospitalizations.

In this section, you have explored the multifaceted approach to managing sickle cell disease (SCD), encompassing preventive measures, patient education, and psychosocial support.

The crucial role of multidisciplinary care teams in delivering comprehensive care and improving the overall well-being of individuals living with SCD. This holistic approach acknowledges that SCD management goes beyond medical interventions and considers the diverse needs of patients and their families.

7. Patient perspectives (Kato *et al.*, 2018; Kavanagh *et al.*, 2022; McCormick *et al.*, 2021; Salinas Cisneros *et al.*, 2020)

Understanding the impact of sickle cell disease (SCD) on affected individuals is crucial. By listening to their voices, we gain insight into their challenges and the importance of ongoing efforts to improve SCD management. Personal stories and narratives from diverse SCD patients offer a window into their lives, encompassing various ages, backgrounds, and disease severities. Through their stories, patients express the hurdles they face, including painful crises, hospitalizations, and missed opportunities, but also highlight moments of resilience and personal triumphs in their SCD journey. Exploring their treatment experiences reveals insights into conventional methods like pain management, blood transfusions, and medications, alongside emerging therapies and the decision-making processes that shape their hopes for the future of SCD treatment. Examining coping strategies and support systems, such as psychosocial support and patient advocacy, sheds light on how patients maintain a high quality of life despite the challenges posed by SCD.

Additionally, patients' perspectives on healthcare interactions, access to specialized care, and healthcare disparities emphasize the need for equitable treatment access and the significance of their voices in shaping the future of SCD management, reminding us of the human face behind this complex condition. Effective leadership and care for individuals with sickle cell disease (SCD) require medical interventions, robust healthcare policies, research funding, and dedicated advocacy efforts. This section explores the critical role of these factors in improving the lives of those affected by SCD.

8. Future directions (Carden *et al.*, 2019; McCormick *et al.*, 2021; Salinas Cisneros *et al.*, 2020)

The landscape of sickle cell disease (SCD) management is evolving rapidly, and the future holds great promise for individuals living with this condition. This section explores potential developments in SCD management, therapies, and research and areas where further investigation is needed:

- **Gene editing and gene therapy:** Explore the progress of gene editing technologies and gene therapy in moving closer to providing a definitive cure for SCD.

- **Transplantation advances:** Mention developments in hematopoietic stem cell transplantation and its role in curative approaches.
- **Combination therapies:** Consider combining emerging therapies for enhanced efficacy and durability.
- Highlight efforts to advance pain management in SCD:
- **Alternative analgesics:** Discuss ongoing research into alternative pain management strategies, such as novel analgesics and non-pharmacological approaches (Ali *et al.,* 2022).
- **Pain biomarkers:** Explore the potential for identifying biomarkers that enable early intervention and tailored pain management.
- Address initiatives aimed at improving the overall quality of life for individuals with SCD:
- **Psychosocial support:** Highlight the importance of continued psychosocial support programs and the integration of mental health services into SCD care.
- **Patient-centered care:** Discuss the shift toward patient-centered care models prioritizing patient preferences, values, and shared decision-making.

9. Conclusion

In conclusion, our comprehensive review has provided a deep insight into the multifaceted landscape of sickle cell disease (SCD). It has encompassed its historical context, intricate pathophysiology, the evolution of both traditional and cutting-edge management approaches, the importance of holistic care, the influence of healthcare policies, the power of advocacy efforts, and the promising future directions in SCD research and treatment.

This exploration has illuminated several key insights. Firstly, SCD is a profoundly complex genetic disorder, and understanding its nuances is vital for effective management. Secondly, while significant strides have been made in conventional therapies, the emergence of curative approaches, including gene editing and stem cell transplantation, offers great hope for individuals with SCD. Thirdly, comprehensive care that considers not only medical treatment but also psychosocial and socioeconomic aspects is paramount for improved patient outcomes. Lastly, advocacy efforts and policy changes play an indispensable role in addressing healthcare disparities and improving access to quality care for SCD patients.

Our review emphasizes the critical need for ongoing research and collaborative efforts to drive innovation in SCD management, reduce disparities in care delivery, and enhance the overall quality of life for those affected by this condition. It serves as a resounding call to action, a reminder that our mission is far from complete until every individual with SCD can access the best care available, devoid of inequalities, and with the hope of a brighter future.

As we move forward, it is crucial to remember that the story of SCD continues to evolve. With each passing day, new discoveries expand our understanding and redefine the boundaries of what is achievable in SCD care. We call upon researchers, healthcare professionals, policymakers, and advocates to join hands in the spirit of collaboration and determination. Together, we can strive towards a world where sickle cell disease is not merely managed but conquered, where individuals living with SCD can lead healthy, fulfilling lives, and where the promise of a brighter future becomes a reality.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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