Available online on 15.09.2025 at ijmspr.com

International Journal of Medical Sciences and Pharma Research

Open Access to Medical Science and Pharma Research

Open Access **Review Article**

Nitric Oxide Deficiency in Sickle Cell Anemia: Mechanisms and Interventions

* Emmanuel Ifeanyi Obeagu

Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.

Article Info:

Article History:

Received 09 May 2025
Reviewed 07 June 2025
Accepted 25 June 2025
Published 15 Sep 2025

Cite this article as:

Obeagu EI, Nitric Oxide Deficiency in Sickle Cell Anemia: Mechanisms and Interventions, International Journal of Medical Sciences & Pharma Research, 2025; 11(3):1-7 *DOI: http://dx.doi.org/10.22270/ijmspr.v11i3.150*

*Address for Correspondence:

Emmanuel Ifeanyi Obeagu, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe

Abstract

Nitric oxide (NO) deficiency plays a crucial role in the pathophysiology of sickle cell anemia (SCA), contributing to vascular dysfunction and related complications that significantly impact patient health. NO is vital for maintaining endothelial function, regulating vascular tone, and preventing platelet aggregation. In SCA, reduced NO bioavailability results from hemolysis, oxidative stress, and impaired nitric oxide synthase (NOS) activity. These factors lead to vascular issues such as pulmonary hypertension, vaso-occlusive crises, and stroke. This review explores the mechanisms behind NO depletion in SCA and emphasizes how NO deficiency worsens vascular dysfunction. The reduction of NO in SCA is mainly due to the release of cell-free hemoglobin from lysed red blood cells, which scavenges NO, along with increased production of reactive oxygen species (ROS) that break down NO. Additionally, endothelial dysfunction further decreases NO synthesis, creating a vicious cycle of declining NO availability. This causes elevated vascular resistance, impaired blood flow, and a higher risk of thrombotic events, all contributing to the morbidity and mortality observed in SCA patients.

Keywords: Nitric oxide, Sickle cell anemia, Vascular dysfunction, Hemolysis, Therapeutic interventions

Introduction

Sickle cell anemia (SCA) is a genetic disorder characterized by the production of abnormal hemoglobin S (HbS), which causes red blood cells to adopt a sickle shape under low oxygen conditions. This sickling of red blood cells results in blockages within blood vessels, leading to ischemia, pain, and widespread organ damage. Beyond the direct effects of sickled cells, SCA is associated with significant vascular dysfunction, which contributes to many of the disease's complications. One key aspect of this dysfunction is nitric oxide (NO) deficiency, a critical factor that exacerbates the disease's vascular complications. NO plays an essential role in regulating vascular tone, preventing platelet aggregation, and maintaining endothelial function. In SCA, reduced NO bioavailability is implicated in several clinical manifestations, including pulmonary hypertension, stroke, and vaso-occlusive crises [1-2]. The pathophysiology of SCA involves hemolysis, the destruction of red blood cells, which leads to the release of cell-free hemoglobin (Hb) into the bloodstream. This free hemoglobin scavenges NO, directly reducing its availability for vascular smooth muscle cells and endothelial cells. Additionally, oxidative stress, a hallmark of SCA, further decreases NO levels by increasing the production of reactive oxygen species (ROS) that degrade NO. These processes, combined with impaired endothelial nitric oxide synthase (eNOS) function, result in a profound reduction in NO bioavailability, which contributes to endothelial dysfunction and impaired vascular regulation.

NO deficiency has wide-reaching consequences for vascular health in SCA patients. The endothelial dysfunction resulting from decreased NO leads to increased vascular tone, contributing to the development of pulmonary hypertension, a common and life-threatening complication in SCA. Furthermore, the reduced NO levels increase the likelihood of thrombotic events, such as stroke, by impairing the anti-platelet and anti-coagulant properties of the endothelium. Vaso-occlusive crises, which are characterized by painful episodes resulting from blockages in blood vessels, are also exacerbated by the diminished vasodilation capacity associated with NO deficiency. These vascular complications not only contribute to the acute symptoms of SCA but also play a role in the chronic organ damage and reduced life expectancy observed in affected individuals [5]. Given the critical role of NO in maintaining vascular health, restoring NO bioavailability has emerged as a potential therapeutic strategy for managing the vascular dysfunction in SCA. Various approaches have been investigated to address the deficiency of NO in SCA, including supplementation of L-arginine, a precursor to NO, and the use of nitrate therapies, which provide NO or NO-like species. Phosphodiesterase type 5 (PDE5)

inhibitors, such as sildenafil, have also been explored for their ability to enhance NO signaling by preventing the breakdown of cyclic GMP, a secondary messenger in the NO pathway. These interventions aim to restore NO-mediated vasodilation and improve endothelial function, thereby alleviating some of the vascular complications associated with SCA [6-7]. In addition to these pharmacological approaches, gene therapies that target the underlying causes of hemolysis and oxidative stress hold promise for providing a long-term solution to NO deficiency in SCA. By correcting the sickle hemoglobin mutation or increasing the production of fetal hemoglobin (HbF), gene therapy could reduce hemolysis, decrease oxidative stress, and restore normal vascular function. These strategies are still in the experimental phase but offer exciting potential for addressing the root causes of NO depletion and improving vascular health in SCA patients [8]

Mechanisms of Nitric Oxide Deficiency in Sickle Cell Anemia

Nitric oxide (NO) deficiency in sickle cell anemia (SCA) arises through multiple intertwined mechanisms that primarily involve hemolysis, oxidative stress, and endothelial dysfunction. The pathophysiology of NO depletion in SCA is complex, with hemolysis playing a central role in reducing NO bioavailability. The breakdown of red blood cells in SCA leads to the release of cell-free hemoglobin (Hb), which scavenges NO directly. This process is exacerbated by the fact that SCA is characterized by chronic hemolysis, further intensifying the NO depletion.

1. **Hemoglobin Scavenging of Nitric Oxide**:

One of the most prominent mechanisms by which NO is depleted in SCA is through the release of cell-free hemoglobin. In SCA, red blood cells undergo frequent rupture, releasing HbS into the plasma. Free Hb binds to NO with high affinity, forming a stable complex that renders NO unavailable for its biological functions, such as vasodilation and regulation of vascular tone. This scavenging of NO by cell-free hemoglobin impairs endothelial function, leading to increased vascular tone and an increased risk of thrombotic events. The absence of sufficient NO in the bloodstream disrupts normal vascular relaxation, contributing to complications such as pulmonary hypertension and stroke [9].

2. **Oxidative Stress and Reactive Oxygen Species (ROS) Production**:

Oxidative stress is a hallmark of SCA, contributing significantly to NO deficiency through the increased production of reactive oxygen species (ROS). These ROS not only damage cellular components but also degrade NO, reducing its bioavailability. In SCA, elevated levels of ROS are generated as a result of both the chronic hemolysis and the presence of sickled red blood cells. The ROS, particularly superoxide anions, react with NO to form peroxynitrite, a potent oxidant that further exacerbates endothelial injury and worsens vascular dysfunction. The increased oxidative stress thus perpetuates a cycle of reduced NO levels and endothelial dysfunction [10].

3. **Endothelial Nitric Oxide Synthase (eNOS) Dysfunction**:

Another critical mechanism underlying NO deficiency in SCA is impaired endothelial nitric oxide synthase (eNOS) function. eNOS is responsible for synthesizing NO in the endothelium, and its activity is essential for maintaining vascular homeostasis. In SCA, the functionality of eNOS is compromised by the altered metabolic environment and increased oxidative stress. ROS and inflammatory cytokines, which are elevated in SCA, can inhibit eNOS activity by inducing post-translational modifications such as phosphorylation, which reduce its ability to produce NO. Furthermore, the impaired NO synthesis results in a diminished capacity for vasodilation, leading to vascular constriction, endothelial dysfunction, and poor blood flow regulation [11-12].

4. **Hemolysis and Impaired NO Bioavailability**:

Chronic hemolysis in SCA leads to the accumulation of cell-free hemoglobin in the plasma, which not only scavenges NO but also induces endothelial dysfunction through the activation of various signaling pathways. Hemoglobin released during hemolysis has been shown to increase the production of pro-inflammatory mediators, further impairing the vasodilatory response to NO. Additionally, hemolytic products, such as heme and iron, catalyze the production of ROS, thereby amplifying the cycle of oxidative damage and NO depletion. Thus, the interplay between hemolysis, oxidative stress, and endothelial dysfunction creates a vicious cycle that further exacerbates NO deficiency in SCA [13-14].

5. **Impaired Vasodilation and Vascular Tone**:

The reduction in NO bioavailability in SCA impairs the ability of blood vessels to dilate properly, leading to increased vascular tone and higher blood pressure. This is particularly evident in the pulmonary circulation, where NO plays a key role in regulating pulmonary vascular resistance. The loss of NO-mediated vasodilation can lead to pulmonary hypertension, a serious complication that is prevalent in SCA patients. Furthermore, the lack of NO increases the risk of vaso-occlusive crises, where blood flow is obstructed due to the sickling of red blood cells, further compromising vascular health [15-16].

Vascular Consequences of Nitric Oxide Deficiency in Sickle Cell Anemia

Nitric oxide (NO) plays a crucial role in maintaining vascular health by regulating vascular tone, inhibiting platelet aggregation, and enhancing endothelial function. In sickle cell anemia (SCA), the deficiency of NO results in significant vascular consequences, which contribute to the morbidity and mortality associated with the disease. These vascular consequences include increased vascular tone, impaired vasodilation, enhanced platelet aggregation, and a higher risk of thrombotic events, all of which significantly exacerbate the disease's clinical manifestations.

1. **Increased Vascular Tone and Hypertension**:

The depletion of NO in SCA leads to the loss of vasodilation, which is the mechanism by which blood vessels relax and increase their diameter to accommodate blood flow. NO is a potent vasodilator that acts on the smooth muscle cells in blood vessels, signaling them to relax and reduce vascular resistance. In the absence of adequate NO, the blood vessels remain constricted, leading to increased vascular tone and higher blood pressure. This increased tone is particularly pronounced in the pulmonary circulation, contributing to the development of pulmonary hypertension (PH), a serious complication observed in SCA patients. Pulmonary hypertension is associated with right heart failure and significantly impacts the survival and quality of life in SCA patients [17].

2. **Vaso-Occlusive Crises**:

One of the most painful and debilitating complications of SCA is the occurrence of vaso-occlusive crises, where blood flow is obstructed by sickled red blood cells, leading to ischemia and severe pain. NO plays a critical role in regulating blood flow by promoting vasodilation. In the absence of NO, the vessels become stiffer and less responsive to the need for increased blood flow, worsening the tendency of sickled red blood cells to clog small blood vessels. This impairment in blood flow exacerbates the occurrence of vaso-occlusive crises and can lead to organ damage, particularly in the kidneys, liver, and bones. The reduced ability of blood vessels to dilate properly limits the body's capacity to alleviate the obstruction caused by sickled cells [18].

3. **Platelet Aggregation and Thrombosis**:

NO is a natural inhibitor of platelet aggregation, preventing blood clots from forming under normal physiological conditions. In SCA, the deficiency of NO leads to increased platelet activation and aggregation, thereby promoting thrombus formation. The compromised vascular environment in SCA, combined with NO deficiency, increases the risk of thrombotic events such as strokes and deep vein thrombosis. The lack of NO-induced platelet inhibition contributes to the hypercoagulable state that is characteristic of SCA, making affected individuals more susceptible to severe cardiovascular events, including ischemic stroke, a common and devastating complication in children and adults with SCA [19].

4. **Endothelial Dysfunction**:

Endothelial cells line the interior surface of blood vessels and play a pivotal role in regulating vascular tone, blood flow, and clotting. NO is crucial for maintaining endothelial function by promoting the relaxation of smooth muscle cells and reducing inflammation. In SCA, the deficiency of NO results in endothelial dysfunction, characterized by an impaired ability to maintain vascular tone and inhibit inflammatory processes. Endothelial dysfunction is associated with an increased expression of adhesion molecules that facilitate the interaction between endothelial cells and circulating white blood cells, leading to inflammation and further vessel injury. This dysfunction contributes to the chronic vascular complications seen in SCA, including the development of atherosclerosis and increased risk of ischemic events [20].

5. **Increased Risk of Organ Damage**:

The vascular consequences of NO deficiency in SCA not only affect blood flow to vital organs but also promote chronic organ damage. For instance, reduced NO availability in the renal vasculature leads to renal hypoperfusion, which can result in kidney dysfunction and progressive renal damage. Similarly, the impaired vascular regulation in the cerebral and coronary circulations can contribute to cerebrovascular accidents (strokes) and myocardial ischemia. These complications are particularly severe in children and can lead to irreversible damage to organs such as the brain, heart, and kidneys. The cumulative impact of vascular dysfunction also accelerates the progression of other organ damage over time, further reducing the life expectancy of individuals with SCA [21].

6. **Systemic Inflammation and Vascular Remodeling**:

Chronic NO deficiency in SCA is linked to systemic inflammation, which can further contribute to vascular remodeling and endothelial injury. The reduced availability of NO promotes the activation of pro-inflammatory cytokines and increases the expression of adhesion molecules on endothelial cells. These changes facilitate the adhesion of leukocytes to the vessel wall, exacerbating the inflammatory response and contributing to the damage of blood vessels. In addition, chronic inflammation and oxidative stress can lead to vascular remodeling, including thickening of the vessel walls, narrowing of the lumen, and increased stiffness of the arteries. This process further diminishes the ability of blood vessels to respond to changes in blood flow, leading to sustained hypertension and worsening vascular health [22].

Therapeutic Strategies to Restore Nitric Oxide Bioavailability in Sickle Cell Anemia

Restoring nitric oxide (NO) bioavailability in sickle cell anemia (SCA) is a promising therapeutic approach to mitigating the vascular dysfunction and complications associated with the disease. Various strategies have been explored to increase NO levels and improve endothelial function, aiming to alleviate symptoms such as pulmonary hypertension, vaso-occlusive crises, and organ damage. These therapeutic strategies focus on either enhancing NO production, reducing its degradation, or directly supplementing NO. This section reviews the key approaches currently under investigation or in clinical use for restoring NO bioavailability in SCA.

1. **Nitrate Therapy**:

One of the most straightforward strategies to restore NO bioavailability is through the use of nitrate-based therapies. Nitrates, such as nitroglycerin and isosorbide dinitrate, are commonly used to enhance the endogenous production of NO by converting into nitric

oxide or increasing the bioavailability of nitrite, a precursor of NO. These compounds act as NO donors, directly increasing the concentration of NO in the bloodstream. Clinical trials and studies have suggested that nitrate therapy can help reduce the incidence of vaso-occlusive crises and improve pulmonary function in SCA patients. However, their use may be limited by side effects such as tolerance and hypotension, which require careful monitoring and dosing adjustments [23].

2. **L-Arginine Supplementation**:

L-arginine, the amino acid precursor of NO, is essential for the synthesis of NO by endothelial nitric oxide synthase (eNOS). In SCA, L-arginine levels are often depleted due to increased oxidative stress and hemolysis, which impair NO production. Supplementing L-arginine has been shown to improve NO synthesis and endothelial function in various vascular disorders, including SCA. Clinical studies have demonstrated that L-arginine supplementation can improve vascular function, increase blood flow, and reduce markers of inflammation in SCA patients. This approach may also have therapeutic potential for reducing the frequency and severity of vaso-occlusive crises, although long-term efficacy and safety need further investigation [24].

3. **Phosphodiesterase Type 5 Inhibitors (PDE5 Inhibitors)**:

Phosphodiesterase type 5 inhibitors, such as sildenafil and tadalafil, work by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP), a molecule that mediates many of the vascular effects of NO. By preventing the degradation of cGMP, PDE5 inhibitors enhance the effects of NO, promoting vasodilation and reducing vascular tone. In SCA, PDE5 inhibitors have shown potential for improving pulmonary hypertension and increasing exercise capacity. Clinical studies have indicated that PDE5 inhibitors can improve pulmonary vascular function and reduce the risk of complications associated with NO deficiency. These drugs are particularly promising for treating pulmonary hypertension, a common and serious complication of SCA [2].

4. **Antioxidants to Reduce Oxidative Stress**:

Oxidative stress plays a pivotal role in reducing NO bioavailability in SCA by promoting the formation of reactive oxygen species (ROS) that degrade NO. Antioxidant therapies aim to counteract the oxidative damage and preserve NO levels. Vitamin E, ascorbic acid (vitamin C), and other antioxidants have been investigated for their ability to reduce oxidative stress and improve endothelial function in SCA. Some studies have shown that antioxidant supplementation can restore NO bioavailability by neutralizing ROS and improving eNOS activity. However, while antioxidants have shown promise in preclinical models, their clinical efficacy in SCA remains inconclusive, and further studies are required to establish optimal dosing regimens and long-term benefits [26].

5. **Gene Therapy and Stem Cell-Based Approaches**:

More advanced therapeutic strategies, including gene therapy and stem cell-based approaches, hold significant promise for restoring NO bioavailability in SCA. Gene therapy techniques aim to correct the underlying genetic mutations in sickle cell patients, potentially addressing the root cause of hemolysis and NO depletion. For example, the introduction of functional copies of the β-globin gene can reduce hemolysis, thereby decreasing the amount of cell-free hemoglobin available to scavenge NO. Stem cell-based therapies, including hematopoietic stem cell transplantation, have shown potential in treating SCA by replenishing healthy red blood cells, thus reducing the burden of hemolysis and restoring vascular function. While these approaches are still in experimental stages, they represent the future of SCA treatment and may offer a long-term solution for restoring NO bioavailability and improving vascular health [27-28].

6. **Hydroxyurea Therapy**:

Hydroxyurea is a well-established therapeutic agent for SCA, primarily known for its ability to increase fetal hemoglobin (HbF) levels, which reduces the sickling of red blood cells. Recent studies suggest that hydroxyurea may also indirectly restore NO bioavailability by decreasing oxidative stress and improving endothelial function. Hydroxyurea has been shown to reduce the incidence of vaso-occlusive crises, alleviate pain, and improve pulmonary function in SCA patients. By modulating the redox balance and enhancing the antioxidant capacity, hydroxyurea may help protect NO from oxidative degradation, contributing to improved vascular health in SCA [29].

Gene Therapy and Novel Interventions for Restoring Nitric Oxide Bioavailability in Sickle Cell Anemia

Gene therapy and novel interventions represent an exciting frontier in the treatment of sickle cell anemia (SCA), particularly in addressing the underlying causes of nitric oxide (NO) deficiency and its associated vascular complications. Traditional therapies such as NO donors, L-arginine supplementation, and phosphodiesterase inhibitors have been beneficial but do not target the root causes of NO depletion. Gene therapy offers the potential to correct the genetic defects responsible for SCA, which could have long-lasting effects on NO bioavailability, vascular function, and overall patient health. Additionally, innovative approaches, including stem cell-based therapies and CRISPR-Cas9 gene editing, are being explored for their ability to offer more sustainable and potentially curative treatments.

1. **Gene Therapy for Hemoglobin S Modification**:

Gene therapy aims to directly address the root cause of sickle cell anemia, which is the mutation in the β-globin gene that leads to the production of sickle hemoglobin (HbS). By correcting this mutation or introducing a modified form of hemoglobin, gene therapy could not only reduce hemolysis (the breakdown of red blood

cells) but also mitigate the excessive release of cell-free hemoglobin, a primary contributor to NO scavenging. Recent advancements in gene therapy have made it possible to either insert a functional copy of the β-globin gene or induce the production of fetal hemoglobin (HbF), which inhibits sickling and reduces the pathological effects associated with HbS. This modification not only improves red blood cell survival and circulation but also helps restore NO bioavailability by preventing the excessive binding and scavenging of NO by free hemoglobin. Clinical trials investigating gene therapy for SCA, particularly using lentiviral vector-based approaches, have shown promising results in terms of reducing disease symptoms and improving overall vascular function [30].

2. **CRISPR-Cas9 Gene Editing**:

The revolutionary CRISPR-Cas9 gene-editing technology has opened new possibilities for directly correcting the genetic mutations associated with sickle cell disease. By editing the β-globin gene, CRISPR-Cas9 could restore normal hemoglobin production or enhance the expression of fetal hemoglobin, effectively alleviating the sickling process. One of the exciting developments in CRISPR-Cas9 technology is its potential to upregulate HbF expression, which can significantly reduce sickling and improve blood flow in SCA patients. Additionally, CRISPR-Cas9 could be used to knock out genes that lead to hemolysis and the release of cell-free hemoglobin, thus indirectly preserving NO bioavailability. This approach, still in early clinical stages, has the potential to provide a one-time, curative treatment for SCA, offering hope for long-term relief from vascular dysfunction and other complications. However, challenges related to delivery efficiency, off-target effects, and long-term safety need to be carefully evaluated [31].

3. **Stem Cell-Based Therapies**:

Stem cell-based therapies have shown promise in treating sickle cell anemia by replacing defective hematopoietic stem cells with healthy ones, either through allogeneic hematopoietic stem cell transplantation (HSCT) or autologous stem cell therapies. This approach offers a potential cure for SCA by providing patients with a source of normal, non-sickled red blood cells, thereby reducing the effects of hemolysis and increasing NO availability. In particular, the use of gene-edited autologous stem cells, where patients' own stem cells are genetically modified to produce either normal hemoglobin or increased fetal hemoglobin, represents an emerging treatment strategy. These gene-edited stem cells, once transplanted, can give rise to healthy red blood cells that do not sickle, improving overall circulation and restoring endothelial function. Studies have shown that stem cell-based interventions, particularly those using genetically modified stem cells, have the potential to dramatically reduce the need for blood transfusions, alleviate vascular complications, and restore NO bioavailability [32].

4. **Inhibition of Hemolysis and Cell-Free Hemoglobin Scavenging**:

In SCA, hemolysis and the release of cell-free hemoglobin contribute significantly to NO depletion by scavenging NO and leading to endothelial dysfunction. Recent research has focused on developing therapies that target hemolysis or prevent the harmful effects of free hemoglobin. One approach is to use recombinant human hemoglobin-binding proteins, such as haptoglobin and hemopexin, which can bind and clear free hemoglobin from the circulation. This would reduce hemoglobin-induced NO scavenging, thereby preserving NO bioavailability and improving vascular function. Additionally, small molecules that prevent the release of cell-free hemoglobin or inhibit its interaction with endothelial cells are being explored as potential therapeutic agents. These interventions have the potential to reduce the oxidative stress and inflammatory response associated with hemolysis, thereby improving both NO levels and overall vascular health in SCA patients [33-35].

5. **Targeting Inflammation and Oxidative Stress**:

Chronic inflammation and oxidative stress play significant roles in NO deficiency in sickle cell anemia. Therefore, therapeutic strategies aimed at modulating the inflammatory response or reducing oxidative stress could have a profound impact on restoring NO bioavailability. For instance, anti-inflammatory agents such as hydroxyurea, which is already used to treat SCA, may help reduce oxidative stress and improve NO production. Other potential interventions include the use of antioxidants like vitamin E and N-acetylcysteine (NAC), which could scavenge free radicals and protect endothelial cells from damage. By reducing the oxidative environment, these therapies would help maintain the integrity of endothelial nitric oxide synthase (eNOS) activity, ensuring continued NO production. Clinical studies are ongoing to determine the long-term efficacy of such antioxidant therapies in improving vascular function and NO bioavailability in SCA patients [36].

6. **Gene Therapy for NO Synthase Modulation**:

Another potential gene therapy strategy involves directly modifying the genes responsible for NO production. By enhancing the expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for synthesizing NO in blood vessels, researchers aim to increase the endogenous production of NO. This approach could involve gene delivery techniques to introduce more copies of the eNOS gene into endothelial cells or activation of eNOS through pharmacological means. By promoting higher levels of eNOS activity, these therapies could restore NO bioavailability and alleviate the vascular dysfunction associated with SCA. While this approach is still in the experimental phase, it holds significant potential for addressing the root cause of NO depletion in SCA and improving endothelial function [37].

Conclusion

Nitric oxide (NO) deficiency plays a central role in the vascular dysfunction and myriad complications observed in sickle cell anemia (SCA). The mechanisms driving NO depletion, including hemolysis, the release of cell-free hemoglobin, and impaired endothelial nitric oxide synthase (eNOS) activity, significantly contribute to endothelial dysfunction and the pathophysiology of SCA. The resulting vascular consequences, such as impaired blood flow, increased oxidative stress, and inflammation, lead to the characteristic clinical manifestations of the disease, including pain crises, organ damage, and reduced quality of life. Therapeutic strategies aimed at restoring NO bioavailability hold substantial promise in addressing these vascular issues. Approaches such as gene therapy, stem cell-based therapies, and small molecule interventions targeting oxidative stress and hemolysis are emerging as potential treatments that could mitigate NO depletion and its detrimental effects. Gene editing technologies like CRISPR-Cas9, along with the modulation of hemoglobin production or increasing eNOS activity, offer long-term solutions to the root causes of NO deficiency in SCA. Additionally, novel interventions that focus on reducing hemolysis and scavenging free hemoglobin may further enhance NO availability and improve endothelial function.

Conflict of Interest: Author declares no potential conflict of interest with respect to the contents, authorship, and/or publication of this article.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting in this paper are available in the cited references.

Ethics approval: Not applicable.

References

1. Gupta A. Sickle Cell Anemia and Related Hemoglobinopathies. InDecision Making Through Problem Based Learning in Hematology: A Step-by-Step Approach in patients with Anemia 2024: 269-289. Singapore: Springer Nature Singapore. https://doi.org/10.1007/978-981-99-8933-1_21

2. Hassan MS, Nasrin T, Mahalka A, Hoque M, Ali S. A perspective on the genesis, diagnostics, and management of sickle cell disease. Egyptian Journal of Medical Human Genetics. 2024; 25(1):150. https://doi.org/10.1186/s43042-024-00623-1

3. Rajput HS, Kumari M, Talele C, Sajan C, Saggu V, Hadia R. Comprehensive Overview Of Sickle Cell Disease: Global Impact, Management Strategies, And Future Directions. Journal of Advanced Zoology. 2024; 45(1). https://doi.org/10.53555/jaz.v45i1.3390

4. Obeagu EI. Role of Autophagy in Modulating Oxidative Stress in Sickle Cell Disease: A Narrative Review. Int. J. Curr. Res. Chem. Pharm. Sci. 2024;11(8):38-46. https://doi.org/10.23880/hij-16000247

5. Obeagu EI. Redox Regulation of Hemoglobin in Sickle Cell Disease: A Review. Int. J. Curr. Res. Chem. Pharm. Sci. 2024;11(8):13-9.

6. Obeagu EI, Bunu UO, Obeagu GU, Habimana JB. Antioxidants in the management of sickle cell anaemia: an area to be exploited for the wellbeing of the patients. Int Res Med Health Sci. 2023 Sep 11;6:12-7.

7. Xiao R, Li L, Zhang Y, Fang L, Li R, Song D, Liang T, Su X. Reducing carbon and nitrogen loss by shortening the composting duration based on seed germination index (SCD@ GI): feasibilities and challenges. Science of The Total Environment. 2024:172883. https://doi.org/10.1016/j.scitotenv.2024.172883 PMid:38697528

8. Lin W, Lv X, Wang Q, Li L, Zou G. Nitrogen concentration dependent optical defects transition in single crystal diamond through low pressure high temperature annealing. Vacuum. 2025:114329. https://doi.org/10.1016/j.vacuum.2025.114329

9. Wood KC, Granger DN. Sickle cell disease: role of reactive oxygen and nitrogen metabolites. Clinical & Experimental Pharmacology & Physiology. 2007 Sep 1;34(9). https://doi.org/10.1111/j.1440-1681.2007.04639.x PMid:17645642

10. Dijkmans T, Djokic MR, Van Geem KM, Marin GB. Comprehensive compositional analysis of sulfur and nitrogen containing compounds in shale oil using GC× GC-FID/SCD/NCD/TOF-MS. Fuel. 2015; 140:398-406. https://doi.org/10.1016/j.fuel.2014.09.055

11. Muehle M, Asmussen J, Becker MF, Schuelke T. Extending microwave plasma assisted CVD SCD growth to pressures of 400 Torr. Diamond and Related Materials. 2017; 79:150-163. https://doi.org/10.1016/j.diamond.2017.09.013

12. Obeagu EI, Obeagu GU. Immunization strategies for individuals with sickle cell anemia: A narrative review. Medicine. 2024; 103(38):e39756. https://doi.org/10.1097/MD.0000000000039756 PMid:39312357 PMCid:PMC11419550

13. Obeagu EI. Strategies for reducing child mortality due to sickle cell disease in Uganda: a narrative review. Annals of Medicine and Surgery.:10-97.

14. Obeagu EI. Erythropoeitin in sickle cell anaemia: a review. International Journal of Research Studies in Medical and Health Sciences. 2020;5(2):22-8. https://doi.org/10.22259/ijrsmhs.0502004

15. Obeagu EI, Obeagu GU. Malnutrition in sickle cell anemia: prevalence, impact, and interventions: a review. Medicine. 2024 May 17;103(20):e38164. https://doi.org/10.1097/MD.0000000000038164 PMid:38758879 PMCid:PMC11098235

16. Quemada M, Delgado A, Mateos L, Villalobos FJ. Nitrogen fertilization I: The nitrogen balance. InPrinciples of agronomy for sustainable agriculture 2024: 377-401. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-031-69150-8_26

17. Krug EC, Winstanley D. The need for comprehensive and consistent treatment of the nitrogen cycle in nitrogen cycling and mass balance studies: I. Terrestrial nitrogen cycle. Science of the total environment. 2002; 293(1-3):1-29. https://doi.org/10.1016/S0048-9697(01)01133-0 PMid:12109464

18. Zhang CC, Zhou CZ, Burnap RL, Peng L. Carbon/nitrogen metabolic balance: lessons from cyanobacteria. Trends in plant science. 2018; 23(12):1116-1130. https://doi.org/10.1016/j.tplants.2018.09.008 PMid:30292707

19. Enwonwu CO, Xu XX, Turner E. Nitrogen metabolism in sickle cell anemia: free amino acids in plasma and urine. The American journal of the medical sciences. 1990; 300(6):366-371. https://doi.org/10.1097/00000441-199012000-00005 PMid:2264574

20. Borel MJ, Buchowski MS, Turner EA, Peeler BB, Goldstein RE, Flakoll PJ. Alterations in basal nutrient metabolism increase resting energy expenditure in sickle cell disease. American Journal of Physiology-Endocrinology and Metabolism. 1998; 274(2):E357-364. https://doi.org/10.1152/ajpendo.1998.274.2.E357 PMid:9486169

21. Jackson AA. The use of stable isotopes to study nitrogen metabolism in homozygous sickle cell disease. InGenetic factors in nutrition. 1984: 297-315. Academic Press, New York. https://doi.org/10.1016/B978-0-12-715950-8.50024-X PMCid:PMC7131065

22. Schnog JJ, Jager EH, van der Dijs FP, Duits AJ, Moshage H, Muskiet FD, Muskiet FA. Evidence for a metabolic shift of arginine metabolism in sickle cell disease. Annals of Hematology. 2004; 83:371-375. https://doi.org/10.1007/s00277-004-0856-9 PMid:15054669

23. Darghouth D, Koehl B, Madalinski G, Heilier JF, Bovee P, Xu Y, Olivier MF, Bartolucci P, Benkerrou M, Pissard S, Colin Y. Pathophysiology of sickle cell disease is mirrored by the red blood cell metabolome. Blood, The Journal of the American Society of Hematology. 2011; 117(6):e57-66. https://doi.org/10.1182/blood-2010-07-299636 PMid:21135259

24. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, Hazen SL, Vichinsky EP, Morris SM, Gladwin MT. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. Jama. 2005; 294(1):81-90. https://doi.org/10.1001/jama.294.1.81 PMid:15998894 PMCid:PMC2065861

25. Zhou Y, Yu X, Nicely A, Cunningham G, Challa C, McKinley K, Nickel R, Campbell A, Darbari D, Summar M, Majumdar S. Amino acid signature during sickle cell pain crisis shows significant alterations related to nitric oxide and energy metabolism. Molecular genetics and metabolism. 2022; 137(1-2):146-152. https://doi.org/10.1016/j.ymgme.2022.08.004 PMid:36030599

26. D'Alessandro A, Nouraie SM, Zhang Y, Cendali F, Gamboni F, Reisz JA, Zhang X, Bartsch KW, Galbraith MD, Espinosa JM, Gordeuk VR. Metabolic signatures of cardiorenal dysfunction in plasma from sickle cell patients as a function of therapeutic transfusion and hydroxyurea treatment. Haematologica. 2023; 108(12):3418. https://doi.org/10.3324/haematol.2023.283288 PMid:37439373 PMCid:PMC10690926

27. Obeagu EI, Prajapati SK, Maurya SD, Maternal Anemia in the Context of Infectious Diseases during Pregnancy: A Review, International Journal of Medical Sciences and Pharma Research, 2025;11(1):8-13 https://doi.org/10.22270/ijmspr.v11i1.134

28. Obeagu EI, Chukwu PH. Inclusive Healthcare Approaches for HIV-Positive Sickle Cell Disease Patients: A Review. Current Research in Biological Sciences. 2025;1(1):01-8.

29. Obeagu EI, Obeagu GU. Managing gastrointestinal challenges: diarrhea in sickle cell anemia. Medicine. 2024; 103(18):e38075. https://doi.org/10.1097/MD.0000000000038075 PMid:38701274 PMCid:PMC11062666

30. Obeagu EI, Obeagu GU. Living with sickle cell in Uganda: A comprehensive perspective on challenges, coping strategies, and health interventions. Medicine. 2024 Dec 20;103(51):e41062. https://doi.org/10.1097/MD.0000000000041062 PMid:39705436 PMCid:PMC11666137

31. Obeagu EI, Adias TC, Obeagu GU. Advancing life: innovative approaches to enhance survival in sickle cell anemia patients. Annals of Medicine and Surgery. 2024; 86(10):6021-6036. https://doi.org/10.1097/MS9.0000000000002534 PMid:39359845 PMCid:PMC11444627

32. Bell V, Varzakas T, Psaltopoulou T, Fernandes T. Sickle cell disease update: new treatments and challenging nutritional interventions. Nutrients. 2024; 16(2):258. https://doi.org/10.3390/nu16020258 PMid:38257151 PMCid:PMC10820494

33. Khan SA, Damanhouri G, Ali A, Khan SA, Khan A, Bakillah A, Marouf S, Al Harbi G, Halawani SH, Makki A. Precipitating factors and targeted therapies in combating the perils of sickle cell disease---A special nutritional consideration. Nutrition & metabolism. 2016; 13:1-2. https://doi.org/10.1186/s12986-016-0109-7 PMid:27508000 PMCid:PMC4977632

34. Patel S, Patel R, Mukkala SR, Akabari A. Emerging therapies and management approaches in sickle cell disease (SCD): A critical review. Journal of Phytonanotechnology and Pharmaceutical Sciences. 2023; 3(3):1-1. https://doi.org/10.54085/jpps.2023.3.3.3

35. Obeagu EI, Prajapati SK, Maurya SD, Anemia in Pregnancy: Exploring Non-Iron Deficiency Causes, International Journal of Medical Sciences and Pharma Research, 2025;11(1):1-7 https://doi.org/10.22270/ijmspr.v11i1.130

36. Boma PM, Kaponda AA, Panda J, Bonnechère B. Enhancing the management of pediatric sickle cell disease by integrating functional evaluation to mitigate the burden of vaso-occlusive crises. Journal of Vascular Diseases. 2024; 3(1):77-87. https://doi.org/10.3390/jvd3010007

37. Obeagu EI, Chukwu PH. Inclusive Healthcare Approaches for HIV-Positive Sickle Cell Disease Patients: A Review. Current Research in Biological Sciences. 2025;1(1):01-8.