https://doi.org/10.46344/JBINO.2025.v14i03.26

NITRIC OXIDE-MEDIATED VASODILATION: A LIFELINE IN SICKLE CELL PATHOPHYSIOLOGY

***Emmanuel Ifeanyi Obeagu**

Department of Biomedical and Laboratory Science, Africa University, Zimbabwe, E-mail: emmanuelobeagu@yahoo.com, obeague@africau.edu, ORCID: 0000-0002-4538-0161

ABSTRACT

Sickle Cell Disease (SCD) is a complex genetic disorder marked by chronic hemolysis, inflammation, and recurrent vaso-occlusive episodes, leading to significant morbidity and mortality. A growing body of evidence implicates endothelial dysfunction and impaired vasoregulation as central features of SCD pathophysiology. At the core of this vascular dysfunction lies a profound deficiency in nitric oxide (NO), a critical vasodilator that regulates vascular tone, inhibits leukocyte adhesion, and prevents platelet aggregation. The hemolysis inherent to SCD releases cell-free hemoglobin and arginase, both of which disrupt NO synthesis and bioavailability, thereby initiating a cascade of vascular complications. Nitric oxide-mediated vasodilation plays a pivotal role in maintaining endothelial health and preventing the cascade of vaso-occlusion. Reduced NO levels not only impair blood flow but also trigger the expression of adhesion molecules, amplify oxidative stress, and promote a pro-thrombotic environment. This dysfunction results in heightened susceptibility to painful crises, pulmonary hypertension, and multi-organ damage. Consequently, restoring NO signaling has emerged as a therapeutic priority in SCD research and clinical practice.

Keywords: *Nitric oxide, Vasodilation, Sickle cell disease, Endothelial dysfunction, Vaso-occlusion*

Introduction

Sickle Cell Disease (SCD) is a hereditary hemoglobinopathy caused by a single nucleotide mutation in the β-globin gene, resulting in the production of abnormal hemoglobin S (HbS). Under deoxygenated conditions, HbS polymerizes within erythrocytes, causing them to adopt a rigid, sickle-like shape. These deformed cells are prone to hemolysis and obstruct capillaries, leading to ischemia, chronic pain, and multi-organ complications. While the intrinsic red blood cell defect is central to the disease, emerging research underscores the importance of vascular dysfunction, particularly involving nitric oxide (NO), in the propagation of SCD pathophysiology [1-3]. Nitric oxide is a gaseous signaling molecule synthesized from L-arginine by nitric oxide synthase (NOS), primarily endothelial NOS (eNOS) in the vascular endothelium. It plays a critical role in maintaining vascular homeostasis by promoting vasodilation, inhibiting platelet aggregation, reducing leukocyte adhesion, and preventing smooth muscle proliferation. In healthy individuals, NO serves as a gatekeeper of vascular tone and blood flow. However, in SCD, NO bioavailability is markedly reduced due to multiple disease-associated mechanisms, most notably chronic intravascular hemolysis [4-6].

Hemolysis in SCD releases large quantities of free hemoglobin into the plasma, where it rapidly binds and inactivates NO. Concurrently, hemolysis also liberates red blood cell arginase, an enzyme that catabolizes L-arginine, thereby depleting the substrate needed for NO synthesis. The dual effect of NO scavenging and diminished NO production creates a profound state of endothelial dysfunction. This deficit in NO leads to vasoconstriction, increased endothelial permeability, platelet activation, and upregulation of adhesion molecules, setting the stage for repeated vaso-occlusive episodes [7-8]. The consequences of impaired NO signaling extend beyond vascular tone regulation. It contributes significantly to a pro-inflammatory and pro-thrombotic environment, exacerbating chronic pain, pulmonary hypertension, stroke, and organ damage frequently seen in SCD patients. The vascular endothelium, normally a barrier and signaling interface, becomes a site of pathological interaction between sickled cells, leukocytes, and platelets, further promoting vaso-occlusion. These findings have shifted the therapeutic focus toward strategies that enhance NO bioavailability and mitigate endothelial damage [9-10].

Nitric Oxide Signaling and Vascular Homeostasis

Nitric oxide (NO) is a critical signaling molecule involved in the regulation of vascular homeostasis, with its effects primarily mediated through the activation of soluble guanylyl cyclase (sGC) in vascular smooth muscle cells. The synthesis of NO occurs in endothelial cells through the enzymatic activity of endothelial nitric oxide synthase (eNOS), which converts L-arginine to NO and L-citrulline. This process is highly regulated by various stimuli, including shear stress, vasoactive substances, and inflammatory signals. Once produced, NO diffuses across the endothelial cell membrane and enters the smooth muscle cells, where it activates sGC, leading to an increase in cyclic guanosine monophosphate (cGMP) levels. Elevated cGMP activates protein kinase G (PKG), which induces vasodilation by reducing intracellular calcium levels, leading to the relaxation of smooth muscle cells and expansion of the blood vessel lumen [11-13]. The role of NO in maintaining vascular homeostasis extends beyond simple vasodilation. NO is crucial in modulating platelet function by preventing platelet aggregation and activation, a process that is essential in reducing thrombosis and maintaining normal blood flow. Additionally, NO inhibits the adhesion of white blood cells to the endothelial surface by downregulating the expression of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). This anti-inflammatory role of NO is important in preventing excessive leukocyte infiltration, which could otherwise lead to endothelial injury and exacerbate conditions like vasculitis or atherosclerosis [14-16].

Moreover, NO maintains endothelial cell integrity by reducing oxidative stress. Under normal conditions, NO acts as an antioxidant, scavenging reactive oxygen species (ROS) and thereby preventing endothelial cell damage. This is critical in maintaining the balance between oxidative and anti-oxidative forces within the vasculature. In this context, NO can directly influence the activity of other enzymes involved in vascular health, such as superoxide dismutase (SOD) and catalase, both of which neutralize ROS. The ability of NO to prevent excessive ROS production underscores its protective role in vascular homeostasis and its relevance in pathologies where oxidative stress is elevated [17-18]. The NO-cGMP signaling pathway is, however, highly susceptible to dysregulation, especially in diseases such as Sickle Cell Disease (SCD). In SCD, chronic hemolysis releases free hemoglobin, which binds and inactivates NO, leading to a reduction in NO bioavailability. Furthermore, the enzyme arginase, which is released during hemolysis, competes with eNOS for L-arginine, the essential substrate for NO synthesis. This further limits NO production, exacerbating endothelial dysfunction and impairing the vasodilatory response. Additionally, the increased oxidative stress present in SCD promotes the uncoupling of eNOS, further impairing its function and contributing to a vicious cycle of reduced NO availability and increased vascular damage [19-20]. The dysregulation of NO signaling in SCD not only contributes to the classic symptoms of vaso-occlusive crises, but also to the development of chronic complications such as pulmonary hypertension, stroke, and renal damage. The impaired NO-mediated vasodilation leads to an overall prothrombotic, proinflammatory environment, which favors the accumulation of sickled red blood cells, leukocytes, and platelets in the microvasculature. This pathological process results in occlusion of small blood vessels, tissue ischemia, and damage to various organs, making the restoration of NO signaling a promising therapeutic strategy in managing SCD [21-22].

Consequences of NO Deficiency in Sickle Cell Disease (SCD)

Nitric oxide (NO) deficiency in Sickle Cell Disease (SCD) has profound and far-reaching consequences that significantly contribute to the disease's clinical manifestations. NO, a potent vasodilator and anti-inflammatory molecule, plays a pivotal role in maintaining vascular health and preventing pathological events such as thrombosis, oxidative stress, and endothelial cell activation. In SCD, the deficiency of NO is driven by both its inactivation due to the release of free hemoglobin (Hb) during hemolysis and the depletion of L-arginine, its precursor, by the enzyme arginase. These combined effects lead to a cascade of vascular dysfunction that exacerbates the clinical severity of SCD, resulting in a variety of complications ranging from acute vaso-occlusive crises to chronic organ damage [23-24]. One of the most significant consequences of NO deficiency in SCD is impaired vasodilation, which compromises blood flow and contributes to the pathophysiology of vaso-occlusive crises. Under normal conditions, NO is produced by endothelial cells in response to shear stress, acting to relax vascular smooth muscle and promote blood vessel dilation. In the absence of adequate NO, the vasculature becomes prone to constriction, increasing vascular resistance and promoting the formation of microvascular occlusions. These blockages are a hallmark of vaso-occlusive episodes, which are associated with severe pain, ischemia, and tissue damage. In SCD, the abnormal sickled red blood cells, coupled with a lack of sufficient NO, further intensify the likelihood of these blockages, leading to recurrent and debilitating pain crises [25-26].

NO also plays a key role in regulating platelet aggregation and preventing thrombosis. By inhibiting platelet activation and the adhesion of leukocytes to the endothelial lining, NO maintains the smooth flow of blood. However, in SCD, reduced NO levels lead to a pro-thrombotic and pro-inflammatory state, where platelets are more prone to aggregation, and white blood cells adhere more readily to the vessel walls. This contributes to the formation of microthrombi and exacerbates the risk of ischemia, stroke, and other thrombotic complications. Furthermore, the endothelial dysfunction associated with NO deficiency promotes the expression of adhesion molecules such as VCAM-1 and ICAM-1, which further facilitate the interaction between circulating sickled cells, platelets, and leukocytes, perpetuating the cycle of vascular occlusion and inflammation [27]. In addition to its effects on blood flow and thrombosis, NO deficiency in SCD also increases oxidative stress, which further exacerbates endothelial damage. NO, as an antioxidant, is normally involved in scavenging reactive oxygen species (ROS), thereby preventing the damage they cause to endothelial cells. However, when NO is deficient, ROS levels rise, leading to oxidative damage of endothelial cells and the uncoupling of endothelial nitric oxide synthase (eNOS), further reducing NO production. The imbalance between ROS and NO not only accelerates the damage to the blood vessels but also leads to the activation of other pathological pathways, including inflammation and fibrosis. This contributes to the progressive nature of SCD, where repeated vaso-occlusions and chronic endothelial dysfunction increase the risk of organ damage, including in the lungs, kidneys, and brain [28]. Moreover, NO deficiency is associated with the development of pulmonary hypertension (PH), a common and serious complication in SCD. Pulmonary hypertension in SCD is largely attributed to the persistent vasoconstriction and vascular remodeling driven by the lack of NO. Inadequate NO production leads to increased pulmonary vascular resistance, which can cause right heart failure and reduce the overall oxygen-carrying capacity of the blood. In some cases, pulmonary hypertension may precede or worsen other complications such as stroke, contributing to the high morbidity and mortality rates in SCD patients [29].

Therapeutic Strategies Targeting the NO Pathway in Sickle Cell Disease

Given the central role of nitric oxide (NO) in the pathophysiology of Sickle Cell Disease (SCD), therapeutic strategies aimed at restoring or enhancing NO bioavailability have become a promising approach in managing the disease's vascular complications. These strategies focus on increasing NO production, preventing its inactivation, and enhancing its signaling to counteract the vascular dysfunction, inflammation, and thrombosis associated with SCD. Various pharmacological agents, lifestyle modifications, and novel therapies have been explored to target the NO pathway, offering potential improvements in both acute and chronic management of SCD [30].

L-Arginine Supplementation

L-arginine, the precursor required for NO synthesis by endothelial nitric oxide synthase (eNOS), has been a primary target for restoring NO levels in SCD. Supplementing with L-arginine has shown promise in improving NO bioavailability, as it provides the necessary substrate for NO production. Clinical studies have demonstrated that L-arginine supplementation can improve endothelial function, reduce blood pressure, and potentially reduce the frequency of vaso-occlusive crises. Moreover, L-arginine supplementation has been associated with a reduction in pulmonary hypertension in SCD patients, further highlighting its therapeutic potential. However, the clinical results have been mixed, with some studies showing significant benefits, while others suggest only modest improvements, indicating the need for more robust research to establish its efficacy [31].

Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide (iNO) is a more direct approach to enhancing NO availability in the lungs and vascular system. By delivering NO directly to the pulmonary circulation, iNO helps improve pulmonary vasodilation, reduce pulmonary hypertension, and enhance overall oxygenation. Studies have shown that iNO can be beneficial in managing acute pain crises, improving blood flow, and reducing the severity of vaso-occlusion. Additionally, iNO has been used in the acute management of newborns with pulmonary hypertension in SCD, with encouraging results. However, its use is typically confined to hospital settings due to its short half-life and need for specialized equipment. The long-term efficacy and safety of iNO in chronic management of SCD remain areas of ongoing investigation [32].

Nitrate and Nitrite Therapy

Dietary nitrates, found in foods such as beets and leafy greens, are converted into nitrites in the body and subsequently into NO under physiological conditions. This natural NO production pathway has led to the exploration of nitrate/nitrite supplementation as a means of boosting NO levels in SCD patients. Several clinical trials have demonstrated that nitrate/nitrite therapy can increase NO bioavailability, improve endothelial function, and enhance exercise tolerance in SCD patients. Additionally, nitrate therapy may provide benefits in reducing blood pressure and alleviating pulmonary hypertension. As a more natural and accessible alternative to other NO-targeted therapies, nitrate-rich foods or nitrate supplements could be an adjunctive treatment, although further clinical validation is necessary to establish optimal dosing and long-term effects [33].

Phosphodiesterase Type 5 Inhibitors (PDE5i)

Phosphodiesterase type 5 inhibitors (PDE5i), such as sildenafil and tadalafil, work by inhibiting the enzyme that breaks down cyclic guanosine monophosphate (cGMP), a downstream mediator of NO signaling. By enhancing the effects of NO through prolonged cGMP signaling, PDE5 inhibitors can promote vasodilation and reduce pulmonary artery pressure, making them useful in managing pulmonary hypertension in SCD. Sildenafil has been shown to improve pulmonary hemodynamics and exercise capacity in SCD patients with pulmonary hypertension, and similar effects have been observed with tadalafil. PDE5 inhibitors also offer potential therapeutic benefits for alleviating pain crises by improving microcirculation. However, the use of PDE5 inhibitors is often limited by side effects, and long-term studies are required to determine their safety and efficacy in chronic SCD management [34].

Gene Therapy and NO Pathway Modulation

Emerging gene therapy approaches targeting the NO pathway offer potential for more permanent solutions to NO deficiency in SCD. One strategy involves the genetic modification of hematopoietic stem cells to enhance NO production by endothelial cells or to bypass the need for NO altogether. For example, overexpression of eNOS or other molecules involved in the NO pathway may provide a sustainable increase in NO levels, reducing the need for continuous pharmacological intervention. Another potential avenue is the modulation of the arginase enzyme, which competes with eNOS for L-arginine, thus limiting NO synthesis. By inhibiting arginase activity, it may be possible to increase L-arginine availability, thereby enhancing NO production. These gene therapy strategies are still in the experimental stage but hold promise for transforming SCD treatment in the future [35].

Combination Therapies

Given the multifactorial nature of SCD and the complex interactions between NO, hemolysis, inflammation, and oxidative stress, combination therapies targeting multiple pathways are emerging as a comprehensive approach to managing the disease. Combining NO-based therapies with antioxidants, anti-inflammatory agents, and agents that improve red blood cell deformability may offer synergistic effects, improving vascular function and reducing the frequency of vaso-occlusive events. For instance, combining L-arginine supplementation with antioxidants like ascorbic acid or vitamin E could address both NO deficiency and oxidative stress, offering a dual approach to improving endothelial function and reducing vascular damage [36-37].

Conclusion

Nitric oxide (NO) plays a central and indispensable role in maintaining vascular health, and its deficiency is a critical contributor to the pathophysiology of Sickle Cell Disease (SCD). The impaired bioavailability of NO exacerbates several complications in SCD, including vaso-occlusive crises, pulmonary hypertension, endothelial dysfunction, and increased oxidative stress. As such, strategies aimed at restoring or enhancing NO signaling have emerged as promising therapeutic avenues to address the vascular and systemic complications of SCD. Therapeutic interventions, such as L-arginine supplementation, inhaled nitric oxide, nitrate/nitrite therapy, and PDE5 inhibitors, have shown varying degrees of efficacy in improving vascular function, alleviating pain crises, and managing pulmonary hypertension. While these therapies have demonstrated clinical benefits, their effectiveness varies across individuals, and further research is required to establish optimal treatment protocols, assess long-term outcomes, and explore novel approaches, such as gene therapy and combination treatments. These emerging strategies hold the potential for significantly improving the quality of life and clinical outcomes for individuals living with SCD.

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.
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.
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).
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.
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.
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.
9. Wood KC, Granger DN. Sickle cell disease: role of reactive oxygen and nitrogen metabolites. Clinical & Experimental Pharmacology & Physiology. 2007 Sep 1;34(9).
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.
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.
12. Obeagu EI, Obeagu GU. Immunization strategies for individuals with sickle cell anemia: A narrative review. Medicine. 2024; 103(38):e39756.
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.
15. Obeagu EI, Obeagu GU. Malnutrition in sickle cell anemia: prevalence, impact, and interventions: a review. Medicine. 2024 May 17;103(20):e38164.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
27. Obeagu EI, Obeagu GU. Management of diabetes mellitus patients with sickle cell anemia: challenges and therapeutic approaches. Medicine. 2024; 103(17):e37941.
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.
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.
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.
32. Bell V, Varzakas T, Psaltopoulou T, Fernandes T. Sickle cell disease update: new treatments and challenging nutritional interventions. Nutrients. 2024; 16(2):258.
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.
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.
35. 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.
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.

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.