Redox Regulation of Hemoglobin in Sickle Cell Disease: A Review

Article *in* International Journal of Current Research in Chemistry and Pharmaceutical Sciences · September 2024

CITATIONS
0

READS
9

1 author:

Emmanuel Ifeanyi Obeagu
Africa University
2,100 PUBLICATIONS **36,090** CITATIONS

SEE PROFILE

INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 11, Issue 8- 2024

Review Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2024.11.08.002

Redox Regulation of Hemoglobin in Sickle Cell Disease: A Review

***Emmanuel Ifeanyi Obeagu**
Department of Medical Laboratory Science, Kampala International University, Uganda
*Corresponding authour: Emmanuel Ifeanyi Obeagu, Department of Medical Laboratory Science, Kampala International University, Uganda, emmanuelobeagu@yahoo.com,
ORCID: 0000-0002-4538-0161

Abstract

Redox regulation of hemoglobin plays a critical role in the pathophysiology of Sickle Cell Disease (SCD), a genetic disorder marked by the presence of abnormal hemoglobin S (HbS). The altered redox state in SCD contributes significantly to hemoglobin polymerization, oxidative stress, and the resultant cellular and tissue damage, which underlies the clinical complications of the disease. This review explores the mechanisms of redox regulation in SCD, focusing on the generation of reactive oxygen species (ROS), the role of antioxidant defense systems, and the impact of oxidative stress on hemoglobin function. The dysregulation of redox pathways in SCD leads to the formation of oxidative hemoglobin derivatives like methemoglobin, which impairs oxygen delivery and exacerbates sickling of red blood cells (RBCs). Oxidative stress further contributes to hemolysis, endothelial dysfunction, and inflammation, amplifying the disease's severity. This review also highlights potential therapeutic strategies targeting redox regulation, including antioxidant supplementation, pharmacological agents that stabilize hemoglobin's redox state, and gene therapy aimed at correcting the underlying genetic mutation in SCD.

Keywords: Sickle Cell Disease, Hemoglobin S, Redox Regulation, Oxidative Stress, Reactive Oxygen Species

Introduction

Sickle Cell Disease (SCD) is a hereditary hemoglobinopathy characterized by the presence of abnormal hemoglobin S (HbS), which results from a single point mutation in the β-globin gene. This mutation, specifically the substitution of valine for glutamic acid at the sixth position of the β-globin chain, alters the physicochemical properties of hemoglobin, leading to the polymerization of deoxygenated HbS. This polymerization causes red blood cells (RBCs) to assume a sickle shape, which is rigid and prone to causing blockages in small blood vessels. These blockages result in vaso-occlusion, chronic hemolysis, and a variety of severe clinical manifestations, including pain crises, acute chest syndrome, and organ damage. While much of the research on SCD has focused on the structural and genetic aspects of HbS, the role of redox regulation in the disease's pathophysiology is gaining increased attention.[1-5] Redox regulation refers to the control of oxidation-reduction (redox) reactions within the cell, which are vital for maintaining cellular homeostasis. In SCD, the redox balance is disrupted, leading to oxidative stress—a condition characterized by the excessive production of reactive oxygen species (ROS) and the insufficient capacity of antioxidant defense systems to neutralize them. The oxidative stress in SCD exacerbates the sickling of RBCs, contributes to hemolysis, and drives inflammation and endothelial dysfunction. Consequently, understanding the redox mechanisms at play in SCD is crucial for unraveling the complexities of the disease and developing targeted therapeutic interventions.[6-10]

Hemoglobin, the oxygen-carrying protein in RBCs, plays a central role in the redox balance within these cells. In its normal function, hemoglobin undergoes periodic oxidation and reduction as it binds and releases oxygen. However, in SCD, the altered structure of HbS makes it more susceptible to oxidative modifications. This susceptibility is compounded by the chronic hemolysis and ischemia-reperfusion injury that are hallmarks of SCD, leading to an elevated production of ROS. These ROS, in turn, can oxidize hemoglobin, forming methemoglobin—a non-functional form of hemoglobin that cannot bind oxygen effectively. The accumulation of methemoglobin and other oxidized hemoglobin species further impairs oxygen delivery and exacerbates the clinical manifestations of SCD.[11-15] The antioxidant defense systems in SCD patients are often overwhelmed by the continuous production of ROS, leading to a persistent state of oxidative stress. Key antioxidant molecules, such as glutathione, superoxide dismutase (SOD), and catalase, are crucial in neutralizing ROS and maintaining redox homeostasis. However, studies have shown that the levels of these antioxidants are significantly reduced in SCD patients, partly due to the chronic oxidative burden they face. The depletion of these antioxidants not only allows for the accumulation of ROS but also contributes to the oxidative damage to hemoglobin and other cellular components, further driving the pathophysiology of SCD.[16-20]

In addition to the direct oxidative modifications of hemoglobin, the redox imbalance in SCD has broader implications for cellular function. Oxidative stress can activate signaling pathways that lead to inflammation, endothelial activation, and apoptosis, all of which contribute to the complications seen in SCD. For instance, the oxidative damage to RBC membranes increases their rigidity and adhesion to the endothelium, promoting vaso-occlusion. Moreover, the oxidative stress-induced activation of endothelial cells and leukocytes exacerbates the inflammatory response, creating a vicious cycle of damage and dysfunction in SCD.[21-25] Given the central role of redox regulation in the pathogenesis of SCD, therapeutic strategies that target redox pathways hold promise for improving clinical outcomes. Antioxidant therapies, such as supplementation with N-acetylcysteine (NAC) or vitamin E, aim to restore the redox balance by boosting the body's natural defenses against ROS. Additionally, pharmacological agents that stabilize the redox state of hemoglobin or inhibit its polymerization under hypoxic conditions are being explored as potential treatments. Gene therapy, which aims to correct the underlying genetic mutation in SCD,

also has the potential to address the redox imbalance by reducing the production of HbS and consequently decreasing oxidative stress.[26-30] This review aims to provide a comprehensive overview of the redox regulation of hemoglobin in SCD, exploring the mechanisms by which oxidative stress influences hemoglobin function and contributes to disease pathology.

Redox Regulation of Hemoglobin

Hemoglobin, the oxygen-carrying protein in red blood cells (RBCs), undergoes continuous oxidation-reduction (redox) reactions as part of its normal function. In its physiological state, hemoglobin exists primarily in two forms: oxyhemoglobin (Fe2+ bound to O2) and deoxyhemoglobin (Fe2+ unbound to O2). These forms are involved in the reversible binding and release of oxygen. However, hemoglobin can also exist in other redox states, such as methemoglobin (Fe3+), where the iron is oxidized and unable to bind oxygen. The redox state of hemoglobin is crucial for maintaining its functionality and ensuring efficient oxygen transport.[31-35] In Sickle Cell Disease (SCD), the redox regulation of hemoglobin is disrupted due to the presence of hemoglobin S (HbS), which has a propensity to polymerize under deoxygenated conditions. This polymerization is not only a result of the altered structural properties of HbS but is also exacerbated by oxidative modifications. Oxidative stress, driven by excessive production of reactive oxygen species (ROS), leads to the formation of oxidized hemoglobin species, including methemoglobin. The conversion of hemoglobin to methemoglobin impairs its ability to transport oxygen, contributing to the clinical symptoms of SCD, such as tissue hypoxia and pain crises.[36-37] The balance between the oxidized and reduced forms of hemoglobin is tightly regulated under normal conditions, involving various cellular mechanisms and antioxidant systems. Enzymes such as NADH-cytochrome b5 reductase and glutathione reductase play critical roles in reducing methemoglobin back to its functional form. In SCD, however, the increased oxidative stress overwhelms these protective mechanisms, leading to a higher prevalence of methemoglobin and other oxidized derivatives. This imbalance not only affects oxygen delivery but also exacerbates the sickling process, as oxidized hemoglobin can enhance the polymerization of HbS.[38-42]

The impact of redox regulation on hemoglobin function in SCD is multifaceted. Oxidative stress can lead to the oxidation of specific amino acid residues in hemoglobin, further destabilizing its structure and promoting polymerization. For example, oxidation of cysteine residues can lead to the formation of disulfide bonds that contribute to the rigidity and aggregation of HbS. Additionally, the increased production of ROS in SCD can cause oxidative damage to the RBC membrane, further promoting hemolysis and contributing to the overall oxidative burden of the disease.[43-45] The therapeutic implications of redox regulation in SCD are significant. Strategies aimed at reducing oxidative stress and restoring redox balance hold promise for alleviating some of the disease's complications. Antioxidant therapies, such as the use of N-acetylcysteine (NAC) or vitamin E, aim to enhance the body's ability to neutralize ROS and protect hemoglobin from oxidative damage. Additionally, pharmacological agents that stabilize the redox state of hemoglobin or prevent its oxidative modifications are being explored. These approaches could potentially improve hemoglobin function and reduce the severity of symptoms in SCD patients.[46-50]

Antioxidant Defense Mechanisms

The human body is equipped with a complex antioxidant defense system designed to neutralize ROS and prevent oxidative damage. In SCD, however, these defenses are often overwhelmed by the excessive production of ROS. Key components of the antioxidant system include enzymatic antioxidants, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), as well as non-enzymatic antioxidants like glutathione, vitamin E, and vitamin C. These antioxidants work synergistically to scavenge free radicals and repair oxidatively damaged molecules.[51-52] In

SCD, the activity of these antioxidant systems may be impaired, leading to an accumulation of ROS and increased oxidative stress. For instance, studies have shown that the levels of glutathione, a critical intracellular antioxidant, are significantly reduced in SCD patients. This depletion is partly due to the chronic oxidative burden imposed by hemolysis and the continuous generation of ROS. The reduced availability of glutathione impairs the ability of RBCs to detoxify hydrogen peroxide, a major ROS, resulting in further oxidative damage to hemoglobin and other cellular components.[53-54]

Oxidative Stress and Hemoglobin Function

Oxidative stress not only influences the polymerization of HbS but also affects its overall function. The oxidation of HbS can lead to the formation of hemichromes, which are denatured hemoglobin species that can bind to the RBC membrane and promote cell rigidity and adhesion. These oxidative modifications of hemoglobin contribute to the mechanical instability of sickle cells, making them more prone to hemolysis and vaso-occlusion. Furthermore, the presence of oxidized hemoglobin in the bloodstream can trigger an inflammatory response, leading to the activation of endothelial cells and the recruitment of leukocytes, which exacerbate the vaso-occlusive events in SCD.[55-56] The oxidative damage to hemoglobin also impairs its ability to deliver oxygen to tissues effectively. The formation of methemoglobin reduces the oxygen-carrying capacity of RBCs, leading to tissue hypoxia and subsequent ischemic injury. This hypoxia, in turn, can induce further ROS production, creating a vicious cycle of oxidative stress and tissue damage in SCD. The impact of oxidative stress on hemoglobin function highlights the need for therapeutic interventions that can protect hemoglobin from oxidative damage and restore its normal function in SCD patients.[57]

Conclusion

The interplay between oxidative stress and hemoglobin function is central to the pathology of Sickle Cell Disease (SCD), profoundly influencing disease progression and clinical manifestations. Oxidative stress in SCD arises from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, leading to significant oxidative modifications of hemoglobin. These modifications, including the formation of methemoglobin and the promotion of hemoglobin S (HbS) polymerization, contribute to reduced oxygen delivery, increased red blood cell (RBC) destruction, and exacerbation of disease symptoms. Oxidative damage impairs hemoglobin's ability to transport oxygen effectively, resulting in tissue hypoxia and exacerbating the clinical features of SCD, such as pain crises and organ damage. The disruption of redox balance within RBCs creates a cycle of oxidative stress and hemolysis, further complicating the disease and impacting patient quality of life. Understanding these mechanisms is critical for developing targeted therapies that address oxidative damage and improve hemoglobin function.

References

1. Alenzi FQ, AlShaya DS. Biochemical and molecular analysis of the beta-globin gene on Saudi sickle cell anemia. Saudi Journal of Biological Sciences. 2019;26(7):1377-1384.
2. Obeagu EI, Ochei KC, Nwachukwu BN, Nchuma BO. Sickle cell anaemia: a review. Scholars Journal of Applied Medical Sciences. 2015;3(6B):224422-52.
3. Obeagu EI. Erythropoeitin in Sickle Cell Anaemia: A Review. International Journal of Research Studies in Medical and Health Sciences. 2020;5(2):22-28.
4. Obeagu EI. Sickle Cell Anaemia: Haemolysis and Anemia. Int. J. Curr. Res. Chem. Pharm. Sci. 2018;5(10):20-21.
5. Obeagu EI, Muhimbura E, Kagenderezo BP, Uwakwe OS, Nakyeyune S, Obeagu GU. An Update on Interferon Gamma and C Reactive Proteins in Sickle Cell Anaemia Crisis. J Biomed Sci. 2022;11(10):84.
6. Sbodio JI, Snyder SH, Paul BD. Redox mechanisms in neurodegeneration: from

disease outcomes to therapeutic opportunities. Antioxidants & Redox Signaling. 2019;30(11):1450-1499.
7. Kovacic P, Somanathan R. Redox processes in neurodegenerative disease involving reactive oxygen species. Current neuropharmacology. 2012;10(4):289-302.
8. La Rosa P, Petrillo S, Bertini ES, Piemonte F. Oxidative stress in DNA repeat expansion disorders: a focus on NRF2 signaling involvement. Biomolecules. 2020;10(5):702.
9. 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. International Research in Medical and Health Sciences. 2023;6(4):12-17.
10. Obeagu EI, Ogunnaya FU, Obeagu GU, Ndidi AC. Sickle cell anaemia: a gestational enigma. European Journal of Biomedical and Pharmaceutical Sciences. 2023;10((9): 72-75
11. Obeagu EI. An update on micro RNA in sickle cell disease. Int J Adv Res Biol Sci. 2018; 5:157-8.
12. Obeagu EI, Babar Q. Covid-19 and Sickle Cell Anemia: Susceptibility and Severity. J. Clinical and Laboratory Research. 2021;3(5):2768-2487.
13. Obeagu EI. Depression in Sickle Cell Anemia: An Overlooked Battle. Int. J. Curr. Res. Chem. Pharm. Sci. 2023;10(10):41-.
14. Renoux C, Joly P, Faes C, Mury P, Eglenen B, Turkay M, Yavas G, Yalcin O, Bertrand Y, Garnier N, Cuzzubbo D. Association between oxidative stress, genetic factors, and clinical severity in children with sickle cell anemia. The Journal of pediatrics. 2018; 195:228-235.
15. Gueye Tall F, Martin C, Ndour EH, Faes C, Deme Ly I, Pialoux V, Connes P, Gueye PM, Ndiaye Diallo R, Renoux C, Diagne I. Influence of oxidative stress biomarkers and genetic polymorphisms on the clinical severity of hydroxyurea-free senegalese children with sickle cell anemia. Antioxidants. 2020;9(9):863.
16. Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. International journal of molecular sciences. 2021;22(9):4642.
17. Obeagu EI, Obeagu GU. Evaluation of Hematological Parameters of Sickle Cell Anemia Patients with Osteomyelitis in A Tertiary Hospital in Enugu, Nigeria. Journal of Clinical and Laboratory Research.2023;6(1):2768-0487.
18. Obeagu EI, Dahir FS, Francisca U, Vandu C, Obeagu GU. Hyperthyroidism in sickle cell anaemia. Int. J. Adv. Res. Biol. Sci. 2023;10(3):81-89.
19. Swem CA, Ukaejiofo EO, Obeagu EI, Eluke B. Expression of micro RNA 144 in sickle cell disease. Int. J. Curr. Res. Med. Sci. 2018;4(3):26-32.
20. Obeagu EI. Sickle cell anaemia: Historical perspective, Pathophysiology and Clinical manifestations. Int. J. Curr. Res. Chem. Pharm. Sci. 2018;5(11):13-15.
21. Obeagu EI, Obeagu GU. Sickle Cell Anaemia in Pregnancy: A Review. International Research in Medical and Health Sciences. 2023 Jun 10;6(2):10-13.
22. Silva M, Faustino P. From stress to sick (le) and back again–oxidative/antioxidant mechanisms, genetic modulation, and cerebrovascular disease in children with sickle cell anemia. Antioxidants. 2023;12(11):1977.
23. Deng M, Sun J, Peng L, Huang Y, Jiang W, Wu S, Zhou L, Chung SK, Cheng X. Scutellarin acts on the AR-NOX axis to remediate oxidative stress injury in a mouse model of cerebral ischemia/reperfusion injury. Phytomedicine. 2022; 103:154214.
24. Obeagu EI, Mohamod AH. An update on Iron deficiency anaemia among children with congenital heart disease. Int. J. Curr. Res. Chem. Pharm. Sci. 2023;10(4):45-48.
25. Edward U, Osuorji VC, Nnodim J, Obeagu EI. Evaluationof Trace Elements in Sickle Cell Anaemia Patients Attending Imo State Specialist Hospital, Owerri. Madonna University journal of Medicine and Health Sciences ISSN: 2814-3035. 2022 Mar 4;2(1):218-234.
26. Umar MI, Aliyu F, Abdullahi MI, Aliyu MN, Isyaku I, Aisha BB, Sadiq RU, Shariff MI,

Obeagu EI. Assessment Of Factors Precipitating Sickle Cell Crises Among Under 5-Years Children Attending Sickle Cell Clinic Of Murtala Muhammad Specialist Hospital, Kano. blood.;11:16.
27. Obeagu EI. Vaso-occlusion and adhesion molecules in sickle cells disease. Int J Curr Res Med Sci. 2018;4(11):33-35.
28. Liu Z, Zhou T, Ziegler AC, Dimitrion P, Zuo L. Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications. Oxidative medicine and cellular longevity. 2017;2017(1):2525967.
29. Ifeanyi OE, Stella EI, Favour AA. Antioxidants In The Management of Sickle Cell Anaemia. Int J Hematol Blood Disord (Internet) 2018 (cited 2021 Mar 4); 3. Available from: https://symbiosisonlinepublishing. com/hematology/hema tology25. php. 2018 Sep.
30. Buhari HA, Ahmad AS, Obeagu EI. Current Advances in the Diagnosis and Treatment of Sickle Cell Anaemia. APPLIED SCIENCES (NIJBAS). 2023;4(1).
31. Nnodim J, Uche U, Ifeoma U, Chidozie N, Ifeanyi O, Oluchi AA. Hepcidin and erythropoietin level in sickle cell disease. British Journal of Medicine and Medical Research. 2015;8(3):261-5.
32. Obeagu EI. BURDEN OF CHRONIC OSTEOMYLITIS: REVIEW OF ASSOCIATIED FACTORS. Madonna University journal of Medicine and Health Sciences. 2023;3(1):1-6.
33. Obeagu EI, Obeagu GU. Oxidative Damage and Vascular Complications in Sickle Cell Anemia: A Review. Elite Journal of Haematology. 2024;2(3):58-66.
34. Gueye Tall F, Martin C, Ndour EH, Faes C, Deme Ly I, Pialoux V, Connes P, Gueye PM, Ndiaye Diallo R, Renoux C, Diagne I. Influence of oxidative stress biomarkers and genetic polymorphisms on the clinical severity of hydroxyurea-free senegalese children with sickle cell anemia. Antioxidants. 2020;9(9):863.
35. Silva DG, Junior EB, de Souza Torres L, Júnior OR, de Castro Lobo C, Bonini-Domingos CR, De Almeida EA. Relationship between oxidative stress, glutathione S-transferase polymorphisms and hydroxyurea treatment in sickle cell anemia. Blood Cells, Molecules, and Diseases. 2011;47(1):23-28.
36. Consoli V, Sorrenti V, Grosso S, Vanella L. Heme oxygenase-1 signaling and redox homeostasis in physiopathological conditions. Biomolecules. 2021;11(4):589.
37. Aloh GS, Obeagu EI, Okoroiwu IL, Odo CE, Chibunna OM, Kanu SN, Elemchukwu Q, Okpara KE, Ugwu GU. Antioxidant-Mediated Heinz Bodies Levels of Sickle Erythrocytes under Drug-Induced Oxidative Stress. European Journal of Biomedical and Pharmaceutical sciences. 2015;2(1):502-507.
38. Obeagu EI, Obeagu GU. Sickle Cell Anaemia in Pregnancy: A Review. International Research in Medical and Health Sciences. 2023; 6 (2): 10-13.
39. Obeagu EI, Ogbuabor BN, Ikechukwu OA, Chude CN. Haematological parameters among sickle cell anemia patients' state and haemoglobin genotype AA individuals at Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria. International Journal of Current Microbiology and Applied Sciences. 2014;3(3):1000-1005.
40. Ifeanyi OE, Nwakaego OB, Angela IO, Nwakaego CC. Haematological parameters among sickle cell anaemia... Emmanuel Ifeanyi1, et al. pdf• Obeagu. Int. J. Curr. Microbiol. App. Sci. 2014;3(3):1000-1005.
41. Obeagu EI, Opoku D, Obeagu GU. Burden of nutritional anaemia in Africa: A Review. Int. J. Adv. Res. Biol. Sci. 2023;10(2):160-163.
42. Ifeanyi E. Erythropoietin (Epo) Level in Sickle Cell Anaemia (HbSS) With Falciparum Malaria Infection in University Health Services, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria. PARIPEX - INDIAN JOURNAL OF RESEARCH, 2015; 4(6): 258-259
43. Ifeanyi OE, Nwakaego OB, Angela IO, Nwakaego CC. Haematological parameters among sickle cell anaemia patients in steady state and haemoglobin genotype AA individuals at Michael Okpara, University of Agriculture, Umudike, Abia State, Nigeria.

Int. J. Curr. Microbiol. App. Sci. 2014;3(3):1000-1005.
44. Ifeanyi OE, Stanley MC, Nwakaego OB. Comparative analysis of some haematological parameters in sickle cell patients in steady and crisis state at michaelokpara University of agriculture, Umudike, Abia state, Nigeria. Int. J. Curr. Microbiol. App. Sci. 2014;3(3):1046-1050.
45. Ifeanyi EO, Uzoma GO. Malaria and The Sickle Cell Trait: Conferring Selective Protective Advantage to Malaria. J Clin Med Res. 2020; 2:1-4.
46. Obeagu EI, Obeagu GU. Oxidative Damage and Vascular Complications in Sickle Cell Anemia: A Review. Elite Journal of Haematology, 2024; 2 (3).:58-66.
47. Obeagu EI, Obeagu GU. Addressing Myths and Stigmas: Breaking Barriers in Adolescent Sickle Cell Disease Education. Elite Journal of Health Science. 2024;2(2):7-15.
48. Obeagu EI, Obeagu GU. Implications of climatic change on sickle cell anemia: A review. Medicine. 2024 Feb 9;103(6):e37127.
49. Singh P, O'Toole TE, Conklin DJ, Hill BG, Haberzettl P. Endothelial progenitor cells as critical mediators of environmental air pollution-induced cardiovascular toxicity. American Journal of Physiology-Heart and Circulatory Physiology. 2021;320(4):H1440-55.
50. Al-Naama LM, Hassan MA, Mehdi JK. Association of erythrocytes antioxidant enzymes and their cofactors with markers of oxidative stress in patients with sickle cell anemia. Qatar medical journal. 2015;2015(2):14.
51. Obeagu EI. Chromium VI: A Silent Aggressor in Sickle Cell Anemia Pathophysiology. Elite Journal of Haematology, 2024; 2 (3).:81-95.
52. Obeagu EI. Maximizing longevity: erythropoietin's impact on sickle cell anemia survival rates. Annals of Medicine and Surgery. 2024:10-97.
53. Obeagu EI, Ubosi NI, Obeagu GU, Egba SI, Bluth MH. Understanding apoptosis in sickle cell anemia patients: Mechanisms and implications. Medicine. 2024;103(2):e36898.
54. Obeagu EI, Ayogu EE, Anyanwu CN, Obeagu GU. Drug-Drug Interactions in the Management of Coexisting Sickle Cell Anemia and Diabetes. Elite Journal of Health Science. 2024;2(2):1-9.
55. Obeagu EI, Obeagu GU. Dual Management: Diabetes and Sickle Cell Anemia in Patient Care. Elite Journal of Medicine. 2024;2(1):47-56.
56. Wood KC, Hsu LL, Gladwin MT. Sickle cell disease vasculopathy: a state of nitric oxide resistance. Free radical biology and medicine. 2008;44(8):1506-1528.
57. Tewari S, Brousse V, Piel FB, Menzel S, Rees DC. Environmental determinants of severity in sickle cell disease. Haematologica. 2015;100(9):1108.

Access this Article in Online

Website: www.ijcrcps.com

Subject: Haematology

Quick Response Code

DOI: 10.22192/ijcrcps.2024.11.08.002

How to cite this article:
Emmanuel Ifeanyi Obeagu. (2024). Redox Regulation of Hemoglobin in Sickle Cell Disease: A Review. Int. J. Curr. Res. Chem. Pharm. Sci. 11(8): 13-19.
DOI: http://dx.doi.org/10.22192/ijcrcps.2024.11.08.002