Elite Journal of Haematology. Volume 2 Issue 7(2024), Pp. 36-43
https://epjournals.com/journals/EJH

Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis

*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

Vaso-occlusive crisis (VOC) is a painful and debilitating complication of sickle cell anemia (SCA) characterized by the obstruction of blood vessels due to sickled red blood cells (RBCs). Hypoxia, or reduced oxygen availability, plays a pivotal role in the pathogenesis of VOC by triggering a cascade of cellular signaling pathways that promote inflammation, oxidative stress, and endothelial dysfunction. This review explores the mechanisms by which hypoxia induces these signaling changes in SCA, including the activation of hypoxia-inducible factors (HIFs), increased production of reactive oxygen species (ROS), and the subsequent inflammatory responses that contribute to vascular obstruction. The activation of HIFs under hypoxic conditions leads to the transcription of various genes involved in angiogenesis, metabolism, and inflammation, while ROS production exacerbates oxidative damage and promotes inflammatory signaling pathways. The interplay between hypoxia, oxidative stress, and inflammation significantly impairs endothelial function, promoting leukocyte adhesion and enhancing the risk of VOC. Additionally, the metabolic adaptations triggered by hypoxia further contribute to the sickling process, creating a vicious cycle that perpetuates the crisis. Strategies aimed at reducing oxidative stress, modulating inflammatory responses, and improving endothelial function may help mitigate VOC and improve outcomes for patients with SCA.

Keywords*: Vaso-occlusive crisis, sickle cell anemia, hypoxia, hypoxia-inducible factors, signaling pathways, inflammation, oxidative stress.*

Introduction

Sickle cell anemia (SCA) is a hereditary blood disorder characterized by the presence of abnormal hemoglobin S (HbS), which leads to the deformation of red blood cells (RBCs) into a rigid, sickle shape under conditions of low oxygen tension. This sickling process not only affects the oxygen-carrying capacity of the blood but also results in the obstruction of microcirculation, leading to various complications, including vaso-occlusive crisis (VOC). VOC is a painful and often debilitating condition that occurs when sickled RBCs clump together, obstructing blood flow and causing tissue ischemia.[1-5] Hypoxia, or reduced oxygen availability, is a critical trigger for VOC in SCA. Hypoxic conditions can arise due to several factors, including dehydration, infection, high altitudes, and extreme temperatures. These environmental triggers often lead to increased hemoglobin polymerization, resulting in the sickling of RBCs and subsequent microvascular occlusion. The complex interplay between hypoxia and the pathophysiological processes that characterize SCA highlights the importance of understanding hypoxia-induced signaling pathways

Citation: Obeagu EI. Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis. *Elite Journal of Haematology, 2024; 2(7):* 36-43

in the development of VOC.[6-10] One of the key players in the cellular response to hypoxia is hypoxia-inducible factor (HIF), a transcription factor that regulates the expression of genes involved in various physiological processes, including angiogenesis, metabolism, and inflammation. Under normoxic conditions, HIF is rapidly degraded; however, during hypoxia, HIF becomes stabilized and translocates to the nucleus, where it dimerizes with HIF-1β to activate the transcription of target genes. In the context of SCA, HIF activation can have both protective and detrimental effects, depending on the specific cellular context and microenvironment.[11-15]

The activation of HIFs leads to increased expression of several pro-inflammatory cytokines and adhesion molecules, which can exacerbate the inflammatory response in SCA. Hypoxia-induced inflammation plays a crucial role in promoting leukocyte adhesion to the endothelium and amplifying the risk of VOC. This inflammatory milieu, coupled with the oxidative stress induced by hypoxia, creates a vicious cycle that perpetuates the occurrence of VOC and its associated complications.[16-20] Reactive oxygen species (ROS) are another critical component of the hypoxic response in SCA. Hypoxia can lead to increased ROS production, resulting in oxidative stress that damages cellular components, including lipids, proteins, and DNA. In SCA, elevated ROS levels can contribute to endothelial dysfunction, further impairing blood flow and promoting VOC.[21-22]

The interplay between hypoxia, ROS, and endothelial dysfunction is complex. Endothelial cells are essential for maintaining vascular homeostasis, and their dysfunction is a key factor in the development of VOC. Hypoxic conditions can lead to the upregulation of adhesion molecules on endothelial cells, promoting the recruitment and activation of leukocytes. This interaction between activated leukocytes and the endothelium further exacerbates the inflammatory response and contributes to the obstruction of blood vessels.[23-27] In addition to the inflammatory and oxidative stress responses, hypoxia induces various metabolic adaptations in cells. Under low oxygen conditions, cells shift from oxidative phosphorylation to anaerobic glycolysis to meet their energy demands. In SCA, this metabolic shift can lead to the accumulation of lactate and a decrease in intracellular pH, creating an acidic microenvironment that exacerbates oxidative stress and inflammation. Understanding these metabolic adaptations provides valuable insights into the complex interplay between hypoxia and the pathophysiology of VOC.[28-32] The interaction between sickle hemoglobin (HbS) and hypoxia is also critical in the pathogenesis of VOC. Under hypoxic conditions, HbS polymerizes, leading to the sickling of RBCs, which obstructs blood flow and exacerbates the hypoxic environment. This sickling process not only impairs the delivery of oxygen to tissues but also promotes a cycle of inflammation and oxidative stress that further contributes to the severity of VOC. The feedback loop between hypoxia and sickling underscores the importance of targeting these mechanisms to improve patient outcomes.[33-37]

Mechanisms of Hypoxia-Induced Signaling in Vaso-Occlusive Crisis

Hypoxia-inducible factors (HIFs) are crucial mediators of the cellular response to low oxygen levels. HIF-1α, the most prominent isoform, is rapidly stabilized under hypoxic conditions and translocates to the nucleus, where it dimerizes with HIF-1β. This heterodimer binds to hypoxia-responsive elements (HREs) in the promoter regions of target genes, initiating their transcription. In sickle cell anemia (SCA), HIF-1α activation results in the upregulation of various genes that contribute to angiogenesis, erythropoiesis, and metabolic adaptation. However, HIF activation also

promotes the expression of pro-inflammatory cytokines and adhesion molecules, exacerbating inflammation and contributing to the pathogenesis of vaso-occlusive crisis (VOC).[38-42] Hypoxia leads to increased production of reactive oxygen species (ROS), which can result from mitochondrial dysfunction and other cellular processes. Elevated ROS levels in SCA can cause oxidative stress, damaging cellular components and leading to cell dysfunction. In the context of VOC, ROS can activate various signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway, which is central to the inflammatory response. The oxidative environment can enhance the expression of adhesion molecules on endothelial cells, facilitating leukocyte adhesion and promoting microvascular obstruction.[43-47] The interaction between hypoxia, ROS, and inflammation is a central mechanism in the pathogenesis of VOC. Hypoxic conditions can activate inflammatory signaling pathways, particularly the NF-κB pathway, leading to the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines contribute to the recruitment and activation of leukocytes, which adhere to the endothelium and release additional inflammatory mediators, perpetuating the cycle of inflammation and increasing the likelihood of VOC. Moreover, the activation of other pathways, such as the mitogen-activated protein kinase (MAPK) pathway, further amplifies the inflammatory response.[48-50]

Endothelial cells play a critical role in maintaining vascular homeostasis, and hypoxia can lead to endothelial dysfunction in SCA. Under hypoxic conditions, endothelial cells upregulate the expression of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). This upregulation promotes the adhesion of activated leukocytes to the endothelium, facilitating their infiltration into the vascular space. Additionally, hypoxia impairs the production of nitric oxide (NO), a potent vasodilator, contributing to vasoconstriction and reduced blood flow, which exacerbates the risk of VOC.[53-54] Hypoxia induces various metabolic adaptations in cells, with a shift from oxidative phosphorylation to anaerobic glycolysis being a hallmark response. This metabolic shift allows cells to continue producing ATP under low oxygen conditions but also leads to the accumulation of lactate and a decrease in intracellular pH, creating an acidic microenvironment. In SCA, this acidic environment can further promote sickling and enhance oxidative stress, creating a feedback loop that exacerbates the severity of VOC.[55-56] The interaction between hypoxia and sickle hemoglobin (HbS) is a critical aspect of VOC pathogenesis. Under low oxygen conditions, HbS polymerizes, leading to the sickling of RBCs, which obstructs blood flow and further perpetuates hypoxia in the surrounding tissues. This sickling process not only compromises oxygen delivery but also triggers inflammatory responses and promotes the release of additional ROS, creating a vicious cycle that increases the risk of VOC. Targeting the mechanisms that mediate HbS polymerization and sickling in response to hypoxia may provide potential therapeutic benefits.[57-58]

Hypoxia can enhance the activation and recruitment of leukocytes, which play a central role in the inflammatory response associated with VOC. Under hypoxic conditions, leukocytes become activated and release pro-inflammatory cytokines, ROS, and proteolytic enzymes. These factors can further damage the endothelium and exacerbate the inflammatory response. The interaction between activated leukocytes and the endothelium, facilitated by hypoxia-induced adhesion

molecules, promotes the accumulation of inflammatory cells at sites of vascular obstruction, further contributing to the development of VOC.[59] Hypoxia can stimulate the production of thromboxane, a potent vasoconstrictor and promoter of platelet aggregation. In SCA, increased thromboxane levels can contribute to vascular occlusion by promoting platelet activation and aggregation, which further impairs blood flow. The interaction between hypoxia, thromboxane production, and platelet activation underscores the importance of understanding these signaling pathways to develop targeted therapies aimed at reducing the incidence and severity of VOC.[60] MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. Emerging evidence suggests that hypoxia can influence the expression of specific miRNAs involved in the regulation of oxidative stress, inflammation, and endothelial function in SCA. For example, hypoxia-induced miRNAs may modulate the expression of key genes associated with inflammation and adhesion, thereby influencing the pathogenesis of VOC. Further research into the role of miRNAs in hypoxia-induced signaling may reveal novel therapeutic targets for managing VOC in SCA.[61-62]

Conclusion

Hypoxia-induced signaling plays a critical role in the pathogenesis of vaso-occlusive crisis (VOC) in sickle cell anemia (SCA). The interplay between hypoxia, reactive oxygen species (ROS), inflammatory responses, and endothelial dysfunction significantly contributes to the frequency and severity of VOC. The activation of hypoxia-inducible factors (HIFs) leads to the upregulation of various genes involved in inflammation and adhesion, while increased ROS production exacerbates oxidative stress, further impairing vascular function. Additionally, the complex relationship between metabolic adaptations, sickle hemoglobin (HbS) polymerization, and leukocyte activation underscores the multifaceted nature of this condition. Targeting oxidative stress, modulating inflammatory pathways, and improving endothelial function may offer promising approaches for managing VOC and enhancing patient outcomes.

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. Williams TN, Thein SL. Sickle cell anemia and its phenotypes. Annual review of genomics and human genetics. 2018;19(1):113-147.
3. Obeagu EI, Ochei KC, Nwachukwu BN, Nchuma BO. Sickle cell anaemia: a review. Scholars Journal of Applied Medical Sciences. 2015;3(6B):224422-52.
4. Obeagu EI. Erythropoeitin in Sickle Cell Anaemia: A Review. International Journal of Research Studies in Medical and Health Sciences. 2020;5(2):22-28.
5. Obeagu EI. Sickle Cell Anaemia: Haemolysis and Anemia. Int. J. Curr. Res. Chem. Pharm. Sci. 2018;5(10):20-21.
6. 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.

Citation: Obeagu EI. Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis. *Elite Journal of Haematology, 2024; 2(7):* 36-43

7. 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
8. Obeagu EI. An update on micro RNA in sickle cell disease. Int J Adv Res Biol Sci. 2018; 5:157-158.
9. Obeagu EI, Babar Q. Covid-19 and Sickle Cell Anemia: Susceptibility and Severity. J. Clinical and Laboratory Research. 2021;3(5):2768-2487.
10. Obeagu EI. Depression in Sickle Cell Anemia: An Overlooked Battle. Int. J. Curr. Res. Chem. Pharm. Sci. 2023;10(10):41-.
11. Gkaliagkousi E, Ritter J, Ferro A. Platelet-derived nitric oxide signaling and regulation. Circulation research. 2007 Sep 28;101(7):654-662.
12. Tran N, Garcia T, Aniqa M, Ali S, Ally A, Nauli SM. Endothelial nitric oxide synthase (eNOS) and the cardiovascular system: in physiology and in disease states. American journal of biomedical science & research. 2022;15(2):153.
13. 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.
14. 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.
15. Njar VE, Ogunnaya FU, Obeagu EI. Knowledge And Prevalence of The Sickle Cell Trait Among Undergraduate Students Of The University Of Calabar. Prevalence.;5(100):0-5.
16. 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.
17. Obeagu EI. Sickle cell anaemia: Historical perspective, Pathophysiology and Clinical manifestations. Int. J. Curr. Res. Chem. Pharm. Sci. 2018;5(11):13-15.
18. 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.
19. 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.
20. 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.
21. 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.
22. Obeagu EI. Vaso-occlusion and adhesion molecules in sickle cells disease. Int J Curr Res Med Sci. 2018;4(11):33-35.
23. 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.

Citation: Obeagu EI. Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis. *Elite Journal of Haematology, 2024; 2(7):* 36-43

24. Buhari HA, Ahmad AS, Obeagu EI. Current Advances in the Diagnosis and Treatment of Sickle Cell Anaemia. APPLIED SCIENCES (NIJBAS). 2023;4(1).
25. Obeagu EI, Obeagu GU. Hemolysis Challenges for Pregnant Women with Sickle Cell Anemia: A Review. Elite Journal of Haematology. 2024;2(3):67-80.
26. Obeagu EI, Obeagu GU, Hauwa BA. Optimizing Maternal Health: Addressing Hemolysis in Pregnant Women with Sickle Cell Anemia. Journal home page: http://www. journalijiar. com.;12(01).
27. Vilas-Boas W, Cerqueira BA, Zanette AM, Reis MG, Barral-Netto M, Goncalves MS. Arginase levels and their association with Th17-related cytokines, soluble adhesion molecules (sICAM-1 and sVCAM-1) and hemolysis markers among steady-state sickle cell anemia patients. Annals of hematology. 2010; 89:877-882.
28. 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):261-265.
29. Obeagu EI. BURDEN OF CHRONIC OSTEOMYLITIS: REVIEW OF ASSOCIATIED FACTORS. Madonna University journal of Medicine and Health Sciences. 2023;3(1):1-6.
30. 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.
31. Obeagu EI, Obeagu GU. Sickle Cell Anaemia in Pregnancy: A Review. International Research in Medical and Health Sciences. 2023; 6 (2): 10-13.
32. 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.
33. 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.
34. 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.
35. 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
36. Tsikas D. Does the inhibitory action of asymmetric dimethylarginine (ADMA) on the endothelial nitric oxide synthase activity explain its importance in the cardiovascular system? The ADMA paradox. Journal of Controversies in Biomedical Research. 2017;3(1):16-22.
37. Martins R, Knapp S. Heme and hemolysis in innate immunity: adding insult to injury. Current opinion in immunology. 2018; 50:14-20.

Citation: Obeagu EI. Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis. *Elite Journal of Haematology, 2024; 2(7):* 36-43

38. Wu G, Meininger CJ, McNeal CJ, Bazer FW, Rhoads JM. Role of L-arginine in nitric oxide synthesis and health in humans. Amino acids in nutrition and health: Amino acids in gene expression, metabolic regulation, and exercising performance. 2021:167-87.
39. 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.
40. Ifeanyi OE, Stanley MC, Nwakaego OB. Comparative analysis of some haematological parameters in sickle cell patients in steady and crisis state at michael okpara University of agriculture, Umudike, Abia state, Nigeria. Int. J. Curr. Microbiol. App. Sci. 2014;3(3):1046-1050.
41. Ifeanyi EO, Uzoma GO. Malaria and The Sickle Cell Trait: Conferring Selective Protective Advantage to Malaria. J Clin Med Res. 2020; 2:1-4.
42. Obeagu EI, Obeagu GU. Oxidative Damage and Vascular Complications in Sickle Cell Anemia: A Review. Elite Journal of Haematology, 2024; 2 (3).:58-66.
43. Roberts BW, Mitchell J, Kilgannon JH, Chansky ME, Trzeciak S. Nitric oxide donor agents for the treatment of ischemia/reperfusion injury in human subjects: a systematic review. Shock. 2013;39(3):229-339.
44. 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.
45. Obeagu EI, Obeagu GU. Implications of climatic change on sickle cell anemia: A review. Medicine. 2024 Feb 9;103(6):e37127.
46. Obeagu EI. Chromium VI: A Silent Aggressor in Sickle Cell Anemia Pathophysiology. Elite Journal of Haematology, 2024; 2 (3).:81-95.
47. Obeagu EI. Maximizing longevity: erythropoietin's impact on sickle cell anemia survival rates. Annals of Medicine and Surgery. 2024:10-97.
48. Samidurai A, Xi L, Das A, Kukreja RC. Beyond erectile dysfunction: cGMP-specific phosphodiesterase 5 inhibitors for other clinical disorders. Annual review of pharmacology and toxicology. 2023;63(1):585-615.
49. 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.
50. 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.
51. Obeagu EI, Obeagu GU. Dual Management: Diabetes and Sickle Cell Anemia in Patient Care. Elite Journal of Medicine. 2024;2(1):47-56.
52. Obeagu EI, Obeagu GU, Hauwa BA. Optimizing Maternal Health: Addressing Hemolysis in Pregnant Women with Sickle Cell Anemia. Journal home page: http://www. journalijiar. com.;12(01).

Citation: Obeagu EI. Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis. *Elite Journal of Haematology, 2024; 2(7):* 36-43

53. Obeagu EI, Obeagu GU. Synergistic Care Approaches: Integrating Diabetes and Sickle Cell Anemia Management. Elite Journal of Scientific Research and Review. 2024;2(1):51-64.
54. Grzywa TM, Sosnowska A, Matryba P, Rydzynska Z, Jasinski M, Nowis D, Golab J. Myeloid cell-derived arginase in cancer immune response. Frontiers in immunology. 2020; 11:938.
55. Obeagu EI, Obeagu GU. Improving Outcomes: Integrated Strategies for Diabetes and Sickle Cell Anemia. Int. J. Curr. Res. Chem. Pharm. Sci. 2024;11(2):20-9.
56. Obeagu EI, Obeagu GU. The Role of Parents: Strengthening Adolescent Education for Sickle Cell Disease Prevention. Elite Journal of Public Health. 2024;2(1):15-21.
57. Obeagu EI, Obeagu GU. Hemolysis Challenges for Pregnant Women with Sickle Cell Anemia: A Review. Elite Journal of Haematology, 2024; 2 (3).:67-80.
58. Obeagu EI, Obeagu GU. Overcoming Hurdles: Anemia Management in Malaria-Affected Childhood. Elite Journal of Laboratory Medicine. 2024;2(1):59-69.
59. Bontempo P, Capasso L, De Masi L, Nebbioso A, Rigano D. Therapeutic Potential of Natural Compounds Acting through Epigenetic Mechanisms in Cardiovascular Diseases: Current Findings and Future Directions. Nutrients. 2024;16(15):2399.
60. Cao M, Zhao Y, He H, Yue R, Pan L, Hu H, Ren Y, Qin Q, Yi X, Yin T, Ma L. New applications of HBOC-201: a 25-year review of the literature. Frontiers in Medicine. 2021; 8:794561.
61. Brun M, Bourdoulous S, Couraud PO, Elion J, Krishnamoorthy R, Lapoumeroulie C. Hydroxyurea downregulates endothelin-1 gene expression and upregulates ICAM-1 gene expression in cultured human endothelial cells. The Pharmacogenomics Journal. 2003;3(4):215-226.
62. Obeagu EI. Redox Signaling and Vaso-Occlusive Crisis in Sickle Cell Anemia. *Elite Journal of Haematology*, *2024; 2(7):* 26-35

Citation: Obeagu EI. Hypoxia-Induced Signaling in the Pathogenesis of Vaso-Occlusive Crisis. *Elite Journal of Haematology, 2024; 2(7):* 36-43