Available online on 15.07.2024 at ijmspr.com

International Journal of Medical Sciences and Pharma Research

Open Access to Medical Science and Pharma Research

Open Access **Review Article**

Glycocalyx Degradation and Endothelial Dysfunction in Vaso-Occlusion: A Review

Emmanuel Ifeanyi Obeagu *

Department of Medical Laboratory Science, Kampala International University, Uganda

Article Info:

Article History:

Received 23 April 2024
Reviewed 26 May 2024
Accepted 28 June 2024
Published 15 July 2024

*Address for Correspondence:

Emmanuel Ifeanyi Obeagu, Department of Medical Laboratory Science, Kampala International University, Uganda.

Cite this article as:

Obeagu EI, Glycocalyx Degradation and Endothelial Dysfunction in Vaso-Occlusion: A Review, International Journal of Medical Sciences & Pharma Research, 2024; 10(2):41-46
DOI: http://dx.doi.org/10.22270/ijmspr.v10i2.102

Abstract

The endothelial glycocalyx is a crucial component of vascular homeostasis, acting as a protective barrier and regulator of endothelial function. In sickle cell anemia (SCA), the degradation of the glycocalyx significantly contributes to endothelial dysfunction and the pathogenesis of vaso-occlusive crises (VOCs). This review examines the mechanisms of glycocalyx degradation, including the roles of shear stress, enzymatic activity, and oxidative stress. The breakdown of the glycocalyx leads to increased vascular permeability, enhanced cell adhesion, and impaired nitric oxide (NO) production, all of which exacerbate endothelial dysfunction and promote VOCs. Mechanistically, shear stress and mechanical forces from altered hemodynamics in SCA disrupt the glycocalyx. Enzymes like heparanase, hyaluronidase, and matrix metalloproteinases degrade glycocalyx components, while oxidative stress from chronic inflammation and hemolysis further accelerates this process. The resulting endothelial dysfunction manifests as increased permeability, promoting inflammation and cell adhesion, and reduced NO synthesis, leading to vasoconstriction and thrombosis. This pro-thrombotic environment facilitates the adhesion and aggregation of sickled red blood cells (RBCs) and other circulating cells, driving VOCs. Therapeutic strategies targeting glycocalyx preservation and restoration are critical for mitigating endothelial dysfunction in SCA. Approaches include the use of glycocalyx precursors, synthetic mimetics, antioxidant therapy, enzyme inhibitors, and nitric oxide donors. These therapies aim to restore the glycocalyx, reduce oxidative stress, and improve NO bioavailability, thereby reducing the incidence and severity of VOCs. Continued research into these therapeutic interventions is essential for optimizing treatment and improving clinical outcomes for patients with SCA.

Keywords: Glycocalyx, Endothelial Dysfunction, Vaso-Occlusion, Sickle Cell Anemia, Inflammation, Shear Stress, Endothelial Cells

Introduction

Vaso-occlusive crises (VOCs) are a defining feature of sickle cell anemia (SCA), characterized by acute episodes of severe pain resulting from the obstruction of blood flow in the microvasculature. These crises not only cause significant morbidity but also contribute to various complications, including organ damage and increased mortality. The pathophysiology of VOCs involves a complex interplay between sickled red blood cells (RBCs), leukocytes, platelets, and the vascular endothelium. Among the critical yet often underappreciated factors in this process is the endothelial glycocalyx, a crucial component of vascular health.[1-2] The endothelial glycocalyx is a gel-like layer that coats the luminal surface of endothelial cells, composed primarily of proteoglycans, glycoproteins, and glycosaminoglycans. This structure serves multiple essential functions, including maintaining vascular permeability, mediating shear stress-induced mechanotransduction, and providing an anti-adhesive barrier to circulating cells. The integrity of the glycocalyx is vital for normal endothelial function and vascular homeostasis. However, in pathological conditions such as SCA, the glycocalyx undergoes significant degradation, contributing to endothelial dysfunction and the exacerbation of VOCs.[3-4] The degradation process is multifactorial, involving mechanical forces, enzymatic activity, and oxidative stress. Altered hemodynamics and increased shear stress due to the presence of rigid, sickled RBCs disrupt the glycocalyx. Additionally, enzymes such as heparanase, hyaluronidase, and matrix metalloproteinases (MMPs) degrade glycocalyx components, while chronic inflammation and oxidative stress further accelerate this degradation.[5-6]

Shear stress, the frictional force exerted by blood flow, plays a significant role in maintaining glycocalyx integrity under normal physiological conditions. In SCA, however, altered blood flow patterns and increased mechanical forces due to sickled RBCs lead to glycocalyx disruption. This mechanical damage strips the glycocalyx from the endothelial surface, exposing endothelial cells to direct mechanical and inflammatory insults, thereby initiating a cascade of vascular dysfunction.[7-8] Enzymatic degradation of the glycocalyx is another critical factor in SCA. Inflammatory conditions prevalent in SCA upregulate the expression and activity of enzymes such as heparanase, hyaluronidase, and MMPs. These enzymes cleave essential components of the glycocalyx, such as heparan sulfate, hyaluronic acid, and other proteoglycans, leading to its breakdown. This enzymatic activity is further exacerbated by oxidative stress, which enhances enzyme activity and directly damages glycocalyx components through the generation of reactive oxygen species (ROS).[9-11] Oxidative stress is a major contributor to glycocalyx degradation in SCA. ROS generated during chronic inflammation, recurrent hemolysis, and ischemia-reperfusion injury can oxidize glycocalyx components, leading to their structural breakdown. Moreover, oxidative stress increases the activity of glycocalyx-degrading

enzymes, creating a vicious cycle of degradation and endothelial dysfunction. The loss of the glycocalyx amplifies oxidative stress by exposing endothelial cells to increased ROS, further compromising vascular health.[12-13] The impact of glycocalyx degradation on endothelial function is profound. The glycocalyx regulates vascular permeability by acting as a physical barrier. Its degradation increases endothelial permeability, allowing the extravasation of plasma proteins, inflammatory cells, and other circulating factors into the vessel wall and surrounding tissues. This increased permeability promotes inflammation and edema, further compromising vascular integrity and facilitating the adhesion of sickled RBCs and leukocytes to the endothelium, key events in the initiation of VOCs.[14-15]

Enhanced cell adhesion is another consequence of glycocalyx degradation. The anti-adhesive properties of the glycocalyx prevent the binding of circulating cells to the endothelial surface. When the glycocalyx is degraded, adhesion molecules such as P-selectin, E-selectin, and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells become exposed and more accessible. This exposure enhances the adhesion of sickled RBCs, leukocytes, and platelets to the endothelium, promoting microvascular occlusion and the development of VOCs.[16-17] Impaired nitric oxide (NO) production further exacerbates endothelial dysfunction in SCA. NO is a crucial mediator of endothelial function, promoting vasodilation and inhibiting platelet aggregation and leukocyte adhesion. The glycocalyx is essential for NO production as it facilitates the mechanotransduction of shear stress signals to endothelial nitric oxide synthase (eNOS). Glycocalyx degradation disrupts this process, leading to reduced NO synthesis and bioavailability. The resulting NO deficiency contributes to vasoconstriction, increased platelet aggregation, and enhanced endothelial adhesion, all of which are critical factors in the pathogenesis of VOCs.[18-20] Given the pivotal role of glycocalyx degradation in endothelial dysfunction and VOCs, therapeutic strategies targeting glycocalyx preservation and restoration are critical. Potential approaches include the use of glycocalyx precursors, synthetic glycocalyx mimetics, antioxidant therapy, enzyme inhibitors, and nitric oxide donors. These strategies aim to restore the glycocalyx, reduce oxidative stress, and improve NO bioavailability, thereby reducing the incidence and severity of VOCs. [21-23]

Mechanisms of Glycocalyx Degradation

Shear Stress and Mechanical Forces

In healthy vasculature, shear stress exerted by laminar blood flow maintains the structural integrity of the endothelial glycocalyx. This mechanical force stimulates the production of key glycocalyx components and supports its regenerative processes. However, in sickle cell anemia (SCA), the presence of rigid, sickled red blood cells (RBCs) disrupts normal blood flow patterns, increasing mechanical forces on the vascular endothelium. This abnormal shear stress can strip the glycocalyx from the endothelial surface, exposing underlying cells to direct mechanical damage and inflammatory insults. This mechanical degradation initiates a cascade of vascular dysfunction, setting the stage for further glycocalyx breakdown and endothelial impairment.[24-26]

Enzymatic Degradation

Enzymatic degradation is a critical mechanism contributing to glycocalyx loss in SCA. Enzymes such as heparanase, hyaluronidase, and matrix metalloproteinases (MMPs) play significant roles in breaking down the glycocalyx. Heparanase specifically cleaves heparan sulfate proteoglycans, while hyaluronidase targets hyaluronic acid, both essential components of the glycocalyx. MMPs, particularly MMP-9, degrade various structural elements of the glycocalyx. Inflammatory conditions prevalent in SCA upregulate the expression and activity of these enzymes, exacerbating the degradation process. Increased levels of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), further stimulate the production of these enzymes, accelerating glycocalyx breakdown.[27-29]

Oxidative Stress

Oxidative stress is a major driver of glycocalyx degradation in SCA. Reactive oxygen species (ROS), produced during chronic inflammation, recurrent hemolysis, and ischemia-reperfusion injury, directly damage glycocalyx components. ROS can oxidize glycosaminoglycans and proteoglycans, leading to their structural breakdown and functional impairment. Additionally, oxidative stress enhances the activity of glycocalyx-degrading enzymes, creating a vicious cycle of degradation. The oxidative environment in SCA not only directly damages the glycocalyx but also compromises the endothelial cells' ability to regenerate and maintain this crucial structure. This continuous exposure to ROS perpetuates endothelial dysfunction, further promoting vascular complications in SCA.[30-32]

Inflammatory Mediators

Inflammatory mediators play a significant role in glycocalyx degradation. In SCA, chronic inflammation results in the elevated production of cytokines and chemokines, which can directly and indirectly contribute to glycocalyx breakdown. For instance, TNF-α and IL-6 not only upregulate the expression of glycocalyx-degrading enzymes but also induce endothelial cell activation and dysfunction. This activation leads to the shedding of glycocalyx components and a further increase in endothelial permeability. The interaction between inflammatory mediators and endothelial cells exacerbates glycocalyx degradation, promoting a pro-inflammatory and pro-thrombotic state that is conducive to vaso-occlusive events.[33-35]

Endothelial Cell Activation

Endothelial cell activation is both a cause and consequence of glycocalyx degradation. Activated endothelial cells exhibit increased expression of adhesion molecules such as P-selectin, E-selectin, and VCAM-1. These molecules facilitate the adhesion of sickled RBCs, leukocytes, and platelets to the endothelium, promoting microvascular occlusion. The initial degradation of the glycocalyx exposes endothelial cells to circulating inflammatory mediators and mechanical stress, leading to their activation. This activation further compromises the endothelial barrier and promotes additional glycocalyx breakdown, creating a feedback loop that perpetuates endothelial dysfunction and vascular occlusion.[36-38]

Hypoxia and Ischemia-Reperfusion Injury

Hypoxia and ischemia-reperfusion injury, common in SCA due to intermittent blood flow obstruction, contribute significantly to glycocalyx degradation. During hypoxic episodes, the lack of oxygen supply leads to endothelial cell stress and damage. Upon reperfusion, the sudden influx of oxygen generates ROS, exacerbating oxidative stress and glycocalyx degradation. This cycle of hypoxia and reperfusion not only damages the glycocalyx but also triggers inflammatory responses and further endothelial cell activation. The resulting endothelial dysfunction and increased vascular permeability contribute to the pathogenesis of vaso-occlusive crises.[39-41]

Hyperviscosity

Hyperviscosity, a characteristic of SCA, also plays a role in glycocalyx degradation. Increased blood viscosity due to high concentrations of sickled RBCs and other cellular elements

results in abnormal shear stress and mechanical forces on the endothelium. These forces disrupt the glycocalyx, leading to its mechanical degradation. Hyperviscosity also slows down blood flow, promoting local hypoxia and the subsequent generation of ROS. The combined effects of mechanical stress and oxidative damage contribute to the progressive loss of glycocalyx integrity in SCA patients.[42-44]

Genetic and Epigenetic Factors

Genetic and epigenetic factors may influence the susceptibility to glycocalyx degradation in SCA. Variations in genes encoding for glycocalyx components, regulatory enzymes, or antioxidant defense mechanisms could affect the resilience of the glycocalyx under stress conditions. Epigenetic modifications, such as DNA methylation and histone acetylation, induced by chronic inflammation and oxidative stress, can alter the expression of genes involved in glycocalyx synthesis and maintenance. Understanding these genetic and epigenetic influences could provide insights into individual variability in glycocalyx integrity and response to therapeutic interventions.[45-47]

Therapeutic Implications

The understanding of mechanisms underlying glycocalyx degradation highlights several potential therapeutic targets. Interventions aimed at reducing oxidative stress, such as antioxidant therapy, can protect the glycocalyx from oxidative damage. Enzyme inhibitors targeting heparanase, hyaluronidase, and MMPs can prevent enzymatic degradation of the glycocalyx. Anti-inflammatory therapies can reduce the production of inflammatory mediators that contribute to glycocalyx breakdown. Additionally, strategies to enhance glycocalyx regeneration and maintenance, such as supplementation with glycocalyx precursors or synthetic mimetics, hold promise for preserving endothelial function and mitigating vascular complications in SCA.[47-50]

Impact on Endothelial Function

Increased Vascular Permeability

One of the most significant impacts of glycocalyx degradation on endothelial function is the increase in vascular permeability. The endothelial glycocalyx serves as a physical barrier that regulates the passage of substances between the bloodstream and surrounding tissues. When the glycocalyx is compromised, endothelial cells become more permeable, allowing plasma proteins, inflammatory cells, and other solutes to extravasate into the interstitial space. This increased permeability contributes to edema and tissue inflammation, exacerbating the conditions that lead to vaso-occlusive crises (VOCs) in sickle cell anemia (SCA). The resulting leakage of fluid and proteins from the vascular compartment into tissues can further impair blood flow and contribute to the pain and complications associated with VOCs.[51-53]

Enhanced Cell Adhesion

The degradation of the glycocalyx also enhances the adhesion of circulating cells to the endothelial surface. Under normal conditions, the glycocalyx acts as an anti-adhesive barrier that prevents the unwanted binding of leukocytes, platelets, and sickled red blood cells (RBCs) to the endothelium. When the glycocalyx is disrupted, endothelial adhesion molecules, such as P-selectin, E-selectin, and vascular cell adhesion molecule-1 (VCAM-1), become more exposed and accessible. This exposure facilitates the adhesion of leukocytes and sickled RBCs to the endothelial cells, promoting microvascular occlusion. The increased adhesion of these cells not only contributes to the development of VOCs but also perpetuates a cycle of inflammation and endothelial dysfunction.[54-56]

Impaired Nitric Oxide Production

Nitric oxide (NO) is a critical mediator of endothelial function, playing a vital role in regulating vascular tone, promoting vasodilation, and inhibiting platelet aggregation and leukocyte adhesion. The endothelial glycocalyx is essential for maintaining NO production as it mediates the mechanotransduction of shear stress signals to endothelial nitric oxide synthase (eNOS). When the glycocalyx is degraded, this mechanotransductive signaling is disrupted, leading to decreased eNOS activity and reduced NO synthesis. The resulting deficiency in NO bioavailability contributes to vasoconstriction, increased platelet aggregation, and enhanced leukocyte adhesion, all of which are critical factors in the pathogenesis of VOCs. The loss of NO signaling further exacerbates endothelial dysfunction and perpetuates the cycle of vaso-occlusion.[57]

Altered Endothelial Cell Function

Glycocalyx degradation leads to altered endothelial cell function, characterized by increased inflammation and impaired vascular responses. Activated endothelial cells release pro-inflammatory cytokines and chemokines, contributing to the recruitment of inflammatory cells and the perpetuation of the inflammatory response. This activation not only promotes leukocyte adhesion but also leads to a pro-thrombotic state, increasing the risk of thrombus formation in the microvasculature. Additionally, the altered endothelial function results in dysregulated vasomotor responses, with impaired vasodilation and increased vasoconstriction contributing to the development of hypoxic regions and further promoting VOCs.[58]

Increased Oxidative Stress

The degradation of the glycocalyx can lead to increased oxidative stress within the endothelial cells. As the protective barrier of the glycocalyx is compromised, endothelial cells become more susceptible to oxidative damage from reactive oxygen species (ROS). Elevated levels of ROS can further damage glycocalyx components and promote a cycle of oxidative stress and endothelial dysfunction. This oxidative environment can exacerbate inflammation, impair NO signaling, and promote the expression of adhesion molecules, all of which contribute to the development of VOCs. The interplay between glycocalyx degradation, oxidative stress, and endothelial dysfunction underscores the importance of addressing these factors in managing SCA.[58]

Impaired Endothelial Repair Mechanisms

The endothelial glycocalyx plays a role in the repair and regeneration of endothelial cells following injury. When the glycocalyx is degraded, the endothelial cells lose their ability to effectively sense and respond to mechanical stimuli, which impairs their regenerative capacity. This inability to repair and regenerate the endothelial surface contributes to chronic endothelial dysfunction and increases the risk of recurrent VOCs. In SCA, where the frequency of vaso-occlusive events is high, compromised endothelial repair mechanisms can lead to cumulative vascular damage over time, further worsening the clinical outcomes for patients.[58]

Dysregulation of Hemostasis

The glycocalyx is involved in maintaining hemostatic balance by regulating the interaction between blood cells and the endothelial surface. When the glycocalyx is degraded, the balance between pro-coagulant and anti-coagulant factors is disrupted, leading to a hypercoagulable state. Increased exposure of pro-coagulant factors and adhesion molecules facilitates platelet activation and aggregation, promoting thrombus formation within the microvasculature. This dysregulation of hemostasis can contribute to the pathogenesis of VOCs and increase the risk of acute complications in SCA, including stroke and acute chest syndrome.[59]

Implications for Clinical Outcomes

The impact of glycocalyx degradation on endothelial function has significant implications for the clinical management of SCA. Understanding the role of glycocalyx integrity in maintaining endothelial health can inform therapeutic strategies aimed at preserving this protective layer. Interventions targeting oxidative stress, inflammation, and glycocalyx restoration may help mitigate endothelial dysfunction, reduce the frequency of VOCs, and improve overall clinical outcomes for patients. By addressing the mechanisms underlying glycocalyx degradation, clinicians can develop more effective treatment strategies and enhance the quality of life for individuals with SCA.[60]

Therapeutic Approaches

Antioxidant Therapy

Given the critical role of oxidative stress in glycocalyx degradation and endothelial dysfunction, antioxidant therapy represents a promising therapeutic approach in sickle cell anemia (SCA). Antioxidants such as vitamins C and E, N-acetylcysteine (NAC), and glutathione have been investigated for their potential to scavenge reactive oxygen species (ROS) and reduce oxidative damage to the glycocalyx. By mitigating oxidative stress, these agents may help preserve glycocalyx integrity, improve endothelial function, and reduce the frequency and severity of vaso-occlusive crises (VOCs). Clinical studies exploring the efficacy of antioxidant supplementation in SCA patients are warranted to determine their potential benefits in clinical practice.[61]

Enzyme Inhibitors

Targeting the enzymes responsible for glycocalyx degradation presents another therapeutic strategy. Inhibitors of heparanase, hyaluronidase, and matrix metalloproteinases (MMPs) may help preserve glycocalyx components and prevent endothelial damage. For example, heparanase inhibitors have shown promise in preclinical studies, suggesting that they can reduce glycocalyx degradation and improve endothelial function. Similarly, MMP inhibitors could mitigate the effects of these enzymes on glycocalyx integrity. Ongoing research is needed to evaluate the safety and efficacy of these enzyme inhibitors in clinical settings and their impact on SCA-related complications.[55]

Glycocalyx Restoration

Therapeutic strategies aimed at restoring the glycocalyx are emerging as a novel approach to managing endothelial dysfunction in SCA. Supplementation with glycocalyx precursors, such as glycosaminoglycans (e.g., hyaluronic acid, chondroitin sulfate), may support the regeneration of the glycocalyx and enhance its protective functions. Additionally, the use of synthetic glycocalyx mimetics designed to mimic the structural and functional properties of the native glycocalyx is being explored. These mimetics can potentially restore the barrier function and anti-adhesive properties of the glycocalyx, thereby reducing endothelial dysfunction and the incidence of VOCs.[56]

Anti-Inflammatory Agents

Since chronic inflammation plays a significant role in glycocalyx degradation and endothelial dysfunction, anti-inflammatory therapies may offer therapeutic benefits in SCA. Agents that inhibit pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), could help reduce the inflammatory burden and protect the glycocalyx from degradation. Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated for their potential to modulate the inflammatory response in SCA, although their use must be carefully considered due to potential side effects. Further research is needed to evaluate the long-term effects of anti-inflammatory therapies on endothelial function and glycocalyx preservation in SCA patients.[57]

Nitric Oxide Donors

Restoring nitric oxide (NO) bioavailability is critical for improving endothelial function in SCA. NO donors, such as sodium nitroprusside and nitroglycerin, can enhance vasodilation and inhibit platelet aggregation, counteracting the effects of glycocalyx degradation. The use of NO donors in conjunction with other therapeutic strategies may provide a multifaceted approach to managing endothelial dysfunction and preventing VOCs. Additionally, pharmacological agents that enhance endogenous NO production, such as phosphodiesterase-5 inhibitors (e.g., sildenafil), may also hold promise in improving vascular function in SCA.[58]

Gene Therapy

Advancements in gene therapy offer the potential for long-term solutions to address the underlying genetic defects in sickle cell anemia. Approaches such as gene editing (e.g., CRISPR-Cas9) or gene transfer using viral vectors could correct the mutation responsible for sickle hemoglobin production. By restoring normal hemoglobin function, these therapies may reduce the formation of sickled RBCs, improve blood flow, and subsequently mitigate glycocalyx degradation and endothelial dysfunction. Although still in the experimental stages, gene therapy represents a groundbreaking avenue for future treatment options in SCA.[59]

Supportive Care and Management

In addition to targeted therapeutic approaches, comprehensive supportive care is essential for managing SCA and its complications. Adequate hydration, pain management, and routine monitoring of patients can help prevent VOCs and support overall vascular health. Patient education on recognizing early signs of VOCs and seeking timely medical attention is also crucial for improving outcomes. Integrating these supportive measures with pharmacological interventions can enhance the effectiveness of therapies aimed at preserving glycocalyx integrity and promoting endothelial function.[60]

Lifestyle Modifications

Encouraging lifestyle modifications can play a supportive role in managing SCA and mitigating endothelial dysfunction. Patients may benefit from dietary interventions rich in antioxidants (e.g., fruits, vegetables) and omega-3 fatty acids, which may help reduce oxidative stress and inflammation. Regular physical activity, tailored to individual capabilities, can also enhance cardiovascular health and promote better blood flow. Additionally, smoking cessation and avoidance of environmental toxins can reduce oxidative burden and improve overall vascular function. Promoting these lifestyle changes alongside medical therapies can contribute to improved endothelial health and reduced risk of VOCs.[61]

Conclusion

Glycocalyx degradation plays a crucial role in the pathogenesis of endothelial dysfunction and vaso-occlusive crises (VOCs) in sickle cell anemia (SCA). The intricate interplay of mechanical forces, oxidative stress, inflammatory mediators, and enzymatic activity contributes to the breakdown of this protective endothelial layer, leading to increased vascular permeability, enhanced cell adhesion, impaired nitric oxide production, and altered endothelial function. These changes create a pro-inflammatory and pro-thrombotic environment that exacerbates the clinical complications associated with SCA.

Addressing glycocalyx degradation through targeted therapeutic approaches offers significant potential for improving endothelial health and reducing the frequency and severity of VOCs. Strategies such as antioxidant therapy, enzyme inhibitors, glycocalyx restoration, anti-inflammatory agents, and nitric oxide donors hold promise for mitigating endothelial dysfunction and enhancing vascular function. Furthermore, emerging therapies such as gene therapy and lifestyle modifications can complement these interventions, providing a multifaceted approach to managing SCA and its complications.

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. https://doi.org/10.1016/j.sjbs.2019.03.003 PMid:31762599 PMCid:PMC6864391

2. Williams TN, Thein SL. Sickle cell anemia and its phenotypes. Annual review of genomics and human genetics. 2018;19(1):113-147. https://doi.org/10.1146/annurev-genom-083117-021320 PMid:29641911 PMCid:PMC7613509

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. https://doi.org/10.22259/ijrsmhs.0502004

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.

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. https://doi.org/10.1161/CIRCRESAHA.107.158410 PMid:17901370

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. https://doi.org/10.34297/AJBSR.2022.15.002087

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. https://doi.org/10.59298/NIJRMS/2023/10.2.1400

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/hematology25. php. 2018 Sep.

24. Buhari HA, Ahmad AS, Obeagu EI. Current Advances in the Diagnosis and Treatment of Sickle Cell Anaemia. APPLIED SCIENCES (NIJBAS). 2023;4(1). https://doi.org/10.59298/NIJBAS/2023/1.1.11111

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. https://doi.org/10.1007/s00277-010-0954-9 PMid:20405289 PMCid:PMC2908460

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. https://doi.org/10.9734/BJMMR/2015/17480

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. https://doi.org/10.15586/jcbmr.2017.22

37. Martins R, Knapp S. Heme and hemolysis in innate immunity: adding insult to injury. Current opinion in immunology. 2018; 50:14-20. https://doi.org/10.1016/j.coi.2017.10.005 PMid:29107115

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. https://doi.org/10.1007/978-3-030-74180-8_10 PMid:34251644

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. https://doi.org/10.37191/Mapsci-2582-4333-2(2)-026

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. https://doi.org/10.1097/SHK.0b013e31827f565b PMid:23358103

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. https://doi.org/10.2147/JBM.S462758 PMid:39081620 PMCid:PMC11288316

45. Obeagu EI, Obeagu GU. Implications of climatic change on sickle cell anemia: A review. Medicine. 2024 Feb 9;103(6):e37127. https://doi.org/10.1097/MD.0000000000037127 PMid:38335412 PMCid:PMC10860944

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. https://doi.org/10.1097/MS9.0000000000001763 PMid:38463100 PMCid:PMC10923353

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. https://doi.org/10.1146/annurev-pharmtox-040122-034745 PMid:36206989

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. https://doi.org/10.1097/MD.0000000000036898 PMid:38215146 PMCid:PMC10783340

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).

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. https://doi.org/10.3389/fimmu.2020.00938 PMid:32499785 PMCid:PMC7242730

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. https://doi.org/10.2147/JBM.S462758 PMid:39081620 PMCid:PMC11288316

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. https://doi.org/10.3390/nu16152399

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. https://doi.org/10.3389/fmed.2021.794561 PMid:34957164 PMCid:PMC8692657

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. https://doi.org/10.1038/sj.tpj.6500176 PMid:12931135