Antioxidants in the Management of Sickle Cell Anaemia: An Area to Be Exploited for the Wellbeing of the Patients

Emmanuel Ifeanyi Obeagu[1*], Umi Omar Bunu[2], Getrude Uzoma Obeagu[3], Jean Bosco Habimana[4]

[1]Department of Medical Laboratory Science, Kampala International University, Uganda.

[2]Department of Public Health, Kampala International University, Uganda.

[3]Department of Nursing Science, Kampala International University, Uganda.

[4]Department of Medical Laboratory Science, Mbarara University of Science and Technology, Uganda.

ABSTRACT

Sickle cell disease (SCD), also known as sickle cell anemia, is an often serious autosomal recessive disorder that occurs when both parents pass the defective gene to their children. When oxygen pressure is low, the biconcave disc shape of red blood cells turns sickle due to the polymerization of defective hemoglobin called HbS, caused by point mutations in the beta-globin gene. In patients with sickle cell disease, red blood cells only last for 10 to 20 days, and the bone marrow cannot replenish them quickly enough. Red blood cells change shape in SCD and become hard, sticky, or sickle-shaped which tends to impede blood flow in the small capillaries. A single nucleotide change (GTG for GAG) in codon six of the globin gene, located on the short arm of chromosome 11, causes sickle cell disease (SCD). As a result, valine displaces glutamic acid at the sixth amino acid position in the globin chain, leading to abnormal production of HbS (sickle hemoglobin), which tends to polymerize under conditions of low oxygen saturation, such as cases occur in the microcirculation. These variables affect the degree of deoxygenation of hemoglobin, pH, intracellular HbF concentration, erythrocyte HbS concentration, and polymerization. Repeated polymerization cycles cause irreversible damage to erythrocyte deformability (RBC), whereas a single polymerization causes a reversible reduction and increased susceptibility to mechanical breakage. The polymerization of HbS is the main factor causing SCD. These variables have an impact on pH, intracellular HbF concentration, erythrocyte HbS concentration, polymerization, and degree of hemoglobin deoxidation. Repeated polymerization cycles cause irreversible damage to red blood cell (RBC) deformity, whereas a single polymerization causes reversible reduction and increased mechanical fragility. As oxygen pressure increases, red blood cells can switch back to this state. The result is followed by a "sickle cell crisis," a vicious cycle that exacerbates hypoxia and leads to more sickle cell disease. Microvascular circulation can be impeded by these deformed sickle cells, leading to vascular damage, organ infarction, pain, and other symptoms of SCD.

Keywords: Antioxidants, Haemoglobin, Management, Red Blood Cells, Sickle Cell Anaemia.

Address of Corresponding Author

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

E-mail: emmanuelobeagu@yahoo.com

Crossref Doi: https://doi.org/10.36437/irmhs.2023.6.4.B

Introduction

Sickle cell disease (SCD), also referred to as sickle cell anemia, is a severe autosomal recessive genetic disease that arises when both parents pass on faulty genes to their offspring.[1-3] In their regular state, RBCs have the shape of a biconcave disc and are free to pass through blood capillaries. The bone marrow is where the RBCs are made, and they typically have a lifespan of about 120 days.[4–7]

When there is low oxygen tension, RBCs' biconcave disc shape changes into a sickle shape as a result of the polymerization of defective hemoglobin known as HbS, which is caused by a

point mutation in the beta-globin gene.[8–9] In SCD patients, RBCs only last 10 to 20 days, and the bone marrow is unable to replenish them quickly enough. As a result, the body produces fewer RBCs and they contain insufficient hemoglobin, which is known as hypochromia. RBCs change shape in SCD, becoming stiff and sticky crescents or sickles that tend to obstruct the flow of blood in tiny capillaries. Ischemia, which is caused by obstructed blood flow, causes slow organ destruction and excruciating agony.[11–12]

Oftentimes, people of African descent and areas with high malaria rates are linked by the sickle cell gene. Along with Africa, it can also be found in the Mediterranean, Middle East, and India.[13–14] Inherited blood disorders like SCD, which affect more than 300,000 babies annually, are categorized as a global health issue by both the World Health Organization (WHO) and the United Nations (UN). This disease is prevalent in most of sub-Saharan Africa, the Middle East, India, the Caribbean, South and Central America, a number of countries along the Mediterranean Sea, the United States, and Europe.[15–16]

Sickle cell disease pathophysiology

A single nucleotide change (GTG for GAG) at codon six of the globin gene, which is located on the short arm of chromosome 11, causes sickle cell disease (SCD). Valine is substituted for glutamic acid at the sixth amino acid position in the globin chain as a result, leading to the production of abnormal HbS (sickle hemoglobin), which has a propensity to polymerize in conditions of low oxygen saturation, such as those that occur in the microcirculation. HbS polymerization is the main SCD process. These variables have an impact on the degree of hemoglobin deoxygenation, pH, intracellular HbF concentration, intra-erythrocytic HbS concentration, and polymerization. Repeated polymerization cycles cause irreversible damage to red blood cell (RBC) deformability, whereas a single polymerization causes reversible decrease and increased mechanical fragility. The HbS polymerization process is the main factor in SCD. These variables have an impact on pH, intracellular HbF concentration, intra-erythrocytic HbS concentration, polymerization, and the degree of hemoglobin deoxygenation. Repeated polymerization cycles cause irreversible damage to red blood cell (RBC) deformability, whereas a single polymerization causes reversible decrease and increased mechanical fragility.[17–18]

As the oxygen tension rises, the red blood cell is able to transform back into this state. The red blood cell eventually develops an irreversible sickle and is destroyed by the spleen due to repeated cycles of sickling and unsickling, which weaken the cell's integrity.[19] The microcapillaries quickly become attached to sclerotic cells, which block blood flow to the supplied tissues. The ensuing "sickle cell crises," a vicious cycle of events that worsens deoxygenation and results in more sickling, are the result. The microvascular circulation may become obstructed by these distorted sickle red blood cells, leading to vascular damage, organ infarctions, painful episodes, and other SCD symptoms.[19]

Oxidative stress in sickle cell anaemia

The imbalance between reactive oxygen species (ROS), reactive nitrogen species (RNS), and antioxidant activity or concentration is referred to as oxidative stress. In addition to non-radical oxidants like hydrogen peroxide (H2O2), hypochlorous acid (HClO), and hypobromous acid (HOBr), ROS are produced when molecular oxygen is reduced and include radical species like the weakly reactive superoxide anion radical (O2) and the strongly reactive hydroxyl radical (OH).[17]

The same is true of RNS, which also include less reactive radical substances like nitric oxide (NO) and nitrogen dioxide (NO2) as well as non-radical substances like nitrous acid (HNO2), dinitrogen trioxide (N2O4), and peroxynitrite (ONOO). Numerous crucial intracellular targets' activity and function can be permanently altered by the production of strong oxidizing radicals like the carbonate radical (CO3) and NO2, which are both produced by the interaction of NO and O2. Additionally, peroxynitrite can damage mitochondria and cell membranes and cause DNA strand breaks and apoptosis by oxidizing and nitrating important essential target substances like thiols. Protein, lipid, carbohydrate, and DNA oxidation leads to impaired intracellular signaling,

cellular malfunction, and death when defense mechanisms are unable to stop it.[20]

For the purpose of fending off ROS and RNS, both enzymatic and non-enzymatic defense mechanisms have been created. Non-enzymatic antioxidants include substances like tocopherols, carotenoids, riboflavin, glutathione, and microelements like zinc. Superoxide dismutase (SOD), catalase, glutathione peroxidase (Gpx), glutathione reductase, glutaredoxin (Grx), thioredoxin/thioredoxin reductase system, and peroxiredoxins (Prx) are just a few of the antioxidants that are produced by enzymes.[21]

Due to the high levels of oxidative stress in SCD, levels of both enzymatic and non-enzymatic antioxidants are decreased.[20] There are many different types of non-enzymatic antioxidants that are deficient in the red blood cells, mononuclear cells, and platelets of SCD patients. They include glutathione, vitamin C, vitamin E, -carotene, plasma retinol, and vitamin E. SOD, Gpx, and Cat levels were down in both serum and plasma.[20]

Sickle cell anemia and antioxidants

The identification of the antioxidant properties of vitamins C and E has enabled studies on the wide range of applications for vitamins and other antioxidants. Today, a number of antioxidants are used to treat neurological and cardiac issues as well as diabetes, cancer, and hypertension.[22] They function by preventing the production of potentially dangerous oxidants. Most antioxidants contain aromatic or phenolic rings that donate an atom of hydrogen (H) to free radicals, reducing their oxidative effects and halting the auto-oxidative chain reaction.[19] These antioxidants produce intermediate forms of free radicals, such as alpha-tocophenoxyl and ascorbyl radicals for vitamins E and C, respectively, which are then stabilized by additional antioxidants, resonance delocalization of the electron within an aromatic ring, or quinone structure synthesis. Despite not belonging to the phenolic group, lipoic acid also performs admirably as a hydrogen atom donor, particularly in its dehydrogenated form (dihydrolipoic acid).[22]

Two antioxidants, ascorbic acid and zinc, inhibit the production of free radicals by chelating or opposing transition metals like iron and copper. From glutamine, which functions as a precursor to these molecules, important substances like glutathione are produced. Glutathione can neutralize ROS directly or indirectly by serving as a substrate for glutathione peroxidase and glutathione-S transferase, two potent endogenous antioxidants.[19]

Antioxidants have a variety of roles in SCD and may exert a range of therapeutic effects as a result. As an illustration, vitamin C works intracellularly in a hydrophilic way, whereas vitamin E affects the membrane in a lipophilic way. Antioxidants are anticipated to have a wide range of favorable effects in general, but they might also have unfavorable effects when a high level of ROS is required to trigger apoptosis. The variation in the functional need for antioxidants may have some bearing on how well antioxidant therapy works for SCD patients. Other factors that affect how well an antioxidant performs include its solubility in the food matrix, pH, temperature, activation energy, rate constant, and oxidation-reduction potential.[23]

A possible mechanism of action in sickle cell anaemia

Although ROS are produced in healthy individuals, the body's inherent antioxidant mechanisms also serve to reduce them. A number of genetic modifiers' roles in regulating oxidative stress have been made clear. One of these is the nuclear factor known as erythroid 2-related factor 2 (nrf-2) that increases the transcription of a number of target genes that are responsible for producing innate antioxidants. An increase in the production of free radicals in SCD is caused by an increase in the activity of numerous oxidases, HbS auto-oxidation, the release of haeme iron, and decreases in nitric oxide levels. Studies have also found a decline in the body's own defense mechanisms, such as superoxide dismutase, glutathione peroxidase, catalase, haem oxygenase, glutathione, vitamin C, and vitamin E.[23]

These natural antioxidants may have decreased as a result of the genetic modifications mentioned

earlier. These tip the scales in favor of an increase in free radical circulation, which increases hemolysis, endothelial damage, cell adhesion, hypercoagulability, vaso-occlusion, and altered gene expression via DNA methylation and histone changes.[19]

Antioxidants used in SCD may be able to stop or slow the progression of tissue damage and hemolysis by scavenging free radicals. There are many additional ways that antioxidants can function. For example, phenolic antioxidants (like vitamin E) act in part by raising nrf2 and may have some anti-inflammatory effects via the same mechanism. Through the direct activation of the enzymes responsible for glutathione synthesis, some other antioxidants can also raise glutathione levels. By controlling DNA methylation and histone modification, selenium can directly modify the epigenome to promote anti-inflammatory processes.[19]

A number of antioxidants, including vitamin E, vitamin A, ascorbic acid, and reduced glutathione in the cytosol, stop the production of free radicals that can harm cells. In addition, a few enzymatic reactions deactivate free radical reactions. These decompose hydrogen peroxide and superoxide anion. The locations of the enzymes are frequently close to the oxidant generation sites. In peroxisomes, catalase degrades hydrogen peroxide, or H2O2 (2H2O2 O2 + 2H2O). Superoxide dismutase, found in many different cell types, turns superoxides into the inactive molecule H2O2 (2O2- +2H H2O2 + O). Cytosolic manganese-superoxide dismutase has been found to belong to this group. In addition to protecting cells from cellular damage, glutathione also eliminates oxygen free radicals.[24]

Clinical trials have shown that antioxidants work as an adjuvant therapy to lessen tissue damage caused by cancer treatment and to increase the anti-tumor effects of chemotherapy. The accumulation of free radicals, which results in the oxidation of biological components, is one of the mechanisms of aging.[19]

Sickle cell anemia is known to have a lower total antioxidant status (TAS) due to an increase in the release of oxygen free radicals (OFRs) produced by metabolic processes in the body. Numerous conditions that affect sickle cell patients may increase the release of OFRs to the point where they outweigh the antioxidant status. A sufficient antioxidant dosage will significantly benefit the patients' health. To boost their immune systems and naturally fight off numerous opportunistic infections that increase the release of OFRs, which may cause cell apoptosis and a corresponding shortening of life, the patients should consume foods and fruits high in antioxidants.[24]

Conclusion

Antioxidants, especially those present in food and fruit, can be given orally and have been shown to be very beneficial for the treatment of sickle cell disease. As a result, there will be fewer crises, inflammatory reactions, and shorter patient lives. Patients are advised to eat more nutrient-rich foods and drink more fluids to improve their health and productivity in life. There is hope for those who have sickle cell anemia. It will be used to treat disorders as antioxidant research becomes more active and encouraging. Studies on the application of antioxidants in this condition must be conducted in order to improve the lives of patients with sickle cell anemia. As a result, sickle cell anaemia will have lower economic and human costs.

References

1. Obeagu EI. An update on micro-RNA in sickle cell disease. Int J Adv Res Biol Sci. 2018; 5:157-8. doi: http://dx.doi.org/10.22192/ijarbs.2018.05.10.016
2. 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):502-7.
3. Edward U, Osuorji VC, Nnodim J, Obeagu EI. Evaluation of 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):218-34. https://madonnauniversity.edu.ng/journals/index.php/medicine/article/view/48

4. Patra, P. K., Khodiar, P. K., Bhaskar, L. V. K. S., Mishra, H., & Jha, A. N. (2014). A Hand Book on Sickle Cell Disease. 771, 1–52. https://www.scic.cg.nic.in/pdf/Sickle%20Cell%20Handbook_English.pdf
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. https://www.itmedicalteam.pl/articles/an-update-on-interferon-gamma-and-c-reactive-proteins-in-sickle-cell-anaemia-crisis.pdf
6. Aloh GS, Obeagu EI, Okoroiwu IL, Odo CE, Chibunna OM, Kanu SN, Elemchukwu Q, Okpara KE, Ugwu GU. Antioxidant–Mediated Amelioration of Drug–Induced Oxidative Stress and Methaemoglobinaemia in G6PD–Deficient and Sickle Erythrocytes. European Journal of Biomedical and Pharmaceutical Sciences.2015; 2 (1): 494-501.
7. 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 Jan 10; 8(3):261-5. doi: https://doi.org/10.9734/BJMMR/2015/17480
8. Obeagu EI, Ochei KC, Nwachukwu BN, Nchuma BO. Sickle cell anaemia: a review. Scholars Journal of Applied Medical Sciences. 2015; 3(6B):2244-52. https://saspublishers.com/media/articles/SJAMS_36B_2244-2252.pdf
9. Obeagu EI. Erythropoeitin in Sickle Cell Anaemia: A Review. International Journal of Research Studies in Medical and Health Sciences. 2020; 5(2):22-8. https://www.ijrsmhs.com/pdf/v5-i2/4.pdf
10. 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. https://www.itmedicalteam.pl/articles/an-update-on-interferon-gamma-and-c-reactive-proteins-in-sickle-cell-anaemia-crisis.pdf
11. Obeagu EI. An update on micro RNA in sickle cell disease. Int J Adv Res Biol Sci. 2018; 5:157-8. https://ijarbs.com/pdfcopy/oct2018/ijarbs16.pdf
12. 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. http://ijcrims.com/pdfcopy/mar2018/ijcrims4.pdf
13. Obeagu EI. Sickle cell anaemia: Historical perspective, Pathophysiology and Clinical manifestations. Int. J. Curr. Res. Chem. Pharm. Sci. 2018; 5(11):13-5. http://ijcrcps.com/pdfcopy/nov2018/ijcrcps3.pdf
14. Obeagu EI. Vaso-occlusion and adhesion molecules in sickle cells disease. Int J Curr Res Med Sci. 2018; 4(11):33-5. http://ijcrims.com/pdfcopy/nov2018/ijcrims4.pdf
15. Belini, E., Da Silva, D. G. H., De Souza Torres, L., De Almeida, E. A., Cancado, R. D., Chiattone, C., & Bonini-Domingos, C. R. (2012). Oxidative stress and antioxidant capacity in sickle cell anaemia patients receiving different treatments and medications for different periods of time. Annals of Hematology, 91(4), 479–489. doi: https://doi.org/10.1007/s00277-011-1340-y
16. Chaturvedi, S., & Debaun, M. R. (2016). Evolution of sickle cell disease from a life-threatening disease of children to a chronic disease of adults: The last 40

years. American Journal of Hematology, 91(1), 5–14. doi: https://doi.org/10.1002/ajh.24235

17. Vona, R., Sposi, N. M., Mattia, L., Gambardella, L., Straface, E., & Pietraforte, D. (2021). Sickle cell disease: Role of oxidative stress and antioxidant therapy. Antioxidants, 10(2), 1–27. doi: https://doi.org/10.3390/antiox10020296
18. Edward U, Osuorji VC, Nnodim J, Obeagu EI. Evaluation of Trace Elements in Sickle Cell Anaemia Patients Attending Imo State Specialist Hospital, Owerri. Madonna University journal of Medicine and Health Sciences; 2022 Mar 4; 2(1):218-34. https://madonnauniversity.edu.ng/journals/index.php/medicine/article/view/48/54
19. Bolarinwa, A. B., Oduwole, O., Okebe, J., Ogbenna, A. A., Otokiti, O. E., & Olatinwo, A. T. (2020). Antioxidant supplementation for sickle cell disease. Cochrane Database of Systematic Reviews, 2020(4). doi: https://doi.org/10.1002/14651858.CD013590
20. Radi, R. (2018). Oxygen radicals, nitric oxide, and peroxynitrite: Redox pathways in molecular medicine. Proceedings of the National Academy of Sciences of the United States of America, 115(23), 5839–5848. doi: https://doi.org/10.1073/pnas.1804932115
21. Chirico, E. N., & Pialoux, V. (2012). Role of oxidative stress in the pathogenesis of sickle cell disease. IUBMB Life, 64(1), 72–80. doi: https://doi.org/10.1002/iub.584
22. Ginter, E., Simko, V., & Panakova, V. (2014). Antioxidants in health and disease. Bratislava Medical Journal, 115(10), 603–606. doi: https://doi.org/10.4149/bll_2014_116
23. Kurutas, E. B. (2016). The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. Nutrition Journal, 15(1), 1–23. doi: https://doi.org/10.1186/s12937-016-0186-5
24. Obeagu EI, Ekelozie IS and Anyiam AF, Antioxidants in The Management of Sickle Cell Anaemia,2018, https://symbiosisonlinepublishing.com/hematology/hematology25.php

How to cite this Article: Emmanuel Ifeanyi Obeagu, Umi Omar Bunu, Getrude Uzoma Obeagu, Jean Bosco Habimana; 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; (6-4): 12-17; doi: https://doi.org/10.36437/irmhs.2023.6.4.B
Source of Support: Nil, **Conflict of Interest:** None declared.
Received: 08-07-2023; **Revision:** 24-8-2023; **Accepted:** 4-09-2023