# Oxidative stress in sickle cell disease

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In the 18th century, Priestley, Scheele and Lavoisier discovered oxygen and reported its critical role and toxic effects in living organisms. In the last century, several studies highlighted the importance of biological oxidation for energy production by aerobic organisms, in defense and the elimination of drugs. Oxidation is mediated by oxidants and free radicals, generically called reactive oxygen species (ROS), are formed as a byproduct of the oxygen metabolism. Antioxidant enzymatic and non-enzymatic molecules play a crucial role in maintaining the balance of ROS; an imbalance may lead to attack on all the components of the cell, including proteins, lipids and DNA. Collectively, oxidative stress is described as an imbalance between oxidants/free radicals and antioxidants[1-3].

Recently, several reports have suggested that oxidative stress is a complex mechanism rather than a simple imbalance between the production and elimination of ROS. Oxidants and free radicals are continuously produced in living organisms with endogenous and external sources such as oxygen and nitric oxide [reactive nitrogen species (RNS)]. An increase in the normal redox state of a cell causes toxic effects that may lead to cell and tissue damage. Furthermore, a decrease in free radicals may be harmful, due to their critical role in microbial defense, cell proliferation, apoptosis, migration, inflammatory gene expression and vascular matrix regulation. In addition, free radicals are increasingly recognized as vital messengers in cellular signal transduction in several organisms[3-5].

Sickle cell anemia is an inherited blood disorder affecting approximately 5% of the world's population. This disease results from a mutation in the beta globin chain inducing the substitution of Val for Glu at position 6, shifting the isoelectric point of the protein[6]. This single mutation induces the production of hemoglobin S (Hb S), which is abnormal and insoluble. Sickle cell disease promotes harmful pathological effects that includes sickling of erythrocytes, vaso-occlusion and ischemia-reperfusion injury. Increasing evidence points towards an oxidative stress response responsible for increased pathophysiology of secondary dysfunctions in sickle cell patients[7,8].

Several molecular mechanisms have been proposed to contribute towards a high oxidative burden in sickle cell patients. Some of the mechanisms that disturb the redox state include, the excessive levels of free hemoglobin that catalyze the Fenton reaction[9], the recurrent ischemia-reperfusion injury promoting the activation of the xanthine-xanthine oxidase system[10] and higher autoxidation of Hb S generating superoxide anion radicals and hence hydrogen peroxide[11]. Furthermore, a chronic proinflammatory response in sickle cell patients induced by constant recruitment of neutrophils and monocytes has been shown to play an important role in causing complications[12,13]. ROS and RNS are not only potential markers of sickle cell disease severity but are also important targets for antioxidant therapies[14,15].

Several reports have indicated lower levels of carotenoids, flavonoids, vitamins C and E and zinc (structural component of superoxide dismutase) in sickle cell anemia patients[14]. Nevertheless, no measurable parameters in clinical studies have shown to ameliorate sickle cell disease in patients that received antioxidant supplementation[16]. In contrast, the treatment of erythrocytes from sickle cell anemia patients with the flavonoid quercetin has been shown to provide protection against hemoglobin oxidation and other cellular modifications promoted by peroxides[17]. Henneberg et al.[18] in this issue of the Revista Brasileira e Hematologia e Hemoterapia demonstrate the use of an unspecific probe (2'7'-dichlorfluorescein-diacetate) to qualitatively assess the intracellular redox state of erythrocytes from sickle cell anemia patients. The authors describe the effect of the flavonols quercetin and rutin to reduce intracellular oxidation promoted by peroxide formation in the cells by their established method. Moreover, an additional antioxidant effect was observed in erythrocytes of patients treated with hydroxyurea. Accordingly, further studies are necessary to understand the mechanistic aspects of free radicals and oxidants in sickle cell disease to improve therapies and find better diagnostic tools. The promising results by Henneberg et al.[18] in monitoring the redox state should encourage the investigation of potential biomolecules and antioxidant therapy for sickle cell treatment in combination with drugs that specifically target ROS/RNS production.

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## References


1. Halliwell B, Gutteridge JM. Free radicals in biology and medicine. 4th ed. New York: Oxford University Press; 2007. 888 p.
2. Augusto O. Radicais livres: bons, maus e naturais. São Paulo: Oficina de Textos; 2006. 120 p.
3. Winterboun CC. Reconciling the chemistry and biology of reactive oxygen species. Nat Chem Biol. 2008;4(5):278-86.
4. Augusto O, Sayuri M. Oxygen radicals and related species. In: Pantopoulos K, Schipeer HM. Principles of free radical biomedicine. New York: Nova Science Publishers; 2011.
5. Toledo JC Jr, Augusto O. Connecting the chemical and biological properties of nitric oxide. Chem Res Toxicol. 2012;25(5):975-89.
6. Piccin A. Do we need to test blood donors for sickle cell anaemia? Blood Transfus. 2010;8(3):137-8. Comment on: Blood Transfus. 2010;8(3):199-202.
7. Stuart MJ, Nagel RL. Sickle-cell disease. Lancet. 2004;364(9442): 1343-60. Comment in: Lancet. 2005;365(9457):382-3.
8. Belcher JD, Beckman JD, Balla G, Balla J, Vercellotti G. Heme degradation and vascular injury. Antioxid Redox Signal. 2010;12(2):233-48.
9. Chirico EN, Pialoux V. Role of oxidative stress in the pathogenesis of sickle cell disease. IUBMB Life. 2012;64(1):72-80.
10. Osarogiagbon UR, Choong S, Belcher JD, Vercellotti GM, Paller MS, Hebbel RP. Reperfusion injury pathophysiology in sickle transgenic mice. Blood. 2000;96(1):314-20.
11. Aslan M, Thornley-Brown D, Freeman BA. Reactive species in sickle cell disease. Ann N Y Acad Sci. 2000;899:375-91.
12. Hebbel RP, Morgan WT, Eaton JW, Hedlund BE. Accelerated autoxidation and heme loss due to instability of sickle hemoglobin. Proc Natl Acad Sci U S A. 1988;85(1):237-41.
13. Ramos CL, Pou S, Britigan BE, Cohen MS, Rosen GM. Spin trapping evidence for myeloperoxidase-dependent hydroxyl radical formation by human neutrophils and monocytes. J Biol Chem. 1992;267(12):8307-12.
14. Kiefmann R, Rifkind JM, Nagababu E, Bhattacharya J. Red blood cells induce hypoxic lung inflammation. Blood. 2008;111(10):5205-14. Comment in: Blood. 2008;111(10):4831-2.
15. Nur E, Biemond BJ, Otten HM, Brandjes DP, Schnog JJ; CURAMA Study Group. Oxidative stress in sickle cell disease; pathophysiology and potential implications for disease management. Am J Hematol. 2011;86(6):484-9.
16. Muskiet FA, Muskiet FD, Meiborg G, Schermer JG. Supplementation of patients with homozygous sickle cell disease with zinc, alpha-tocopherol, vitamin C, soybean oil, and fish oil. Am J Clin Nutr. 1991;54(4):736-44.
17. Cesquini M, Torsoni MA, Stoppa GR, Ogo SH. t-BOOH-induced oxidative damage in sickle red blood cells and the role of flavonoids. Biomed Pharmacother. 2003;57(3-4):124-9.
18. Henneberg R, Otuki MF, Furman AE, Hermann P, Nascimento AJ, Leonart MS. Protective effect of flavonoids against reactive oxygen species production in sickle cell anemia patients treated with hydroxyurea. Rev Bras Hematol Hemoter. 2013;35(1):52-5.


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