Symptoms of Sickle Cell Disease in Children Include Oxidative Stress, Antioxidant Efficiency, Biomolecule Damage and Inflammation

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Abstract

The etiology and consequences of sickle cell disease (SCD) are greatly impacted by oxidative stress. At birth, sickle cell is present. A kid is born with sickle cell anaemia if they receive two copies of a sickle cell gene, each from each parent. Endothelial dysfunction and severe inflammation have both been connected to the oxidative stress that is a typical concern for SCD patients. Catalase or superoxide dismutase (SOD) were two antioxidant enzymes that can be helpful in reducing damage. The oxidative processes have a major part in the pathogenesis of the disease. The primary treatment of SCD is blood transfusions, although receiving multiple transfusions at once can lead to iron excess. Patients with SCD lack sufficient evidence linking oxidative stress, hemolyticanemia, or insulin resistance. Hemolytic anaemia, heightened infection risk, and vaso-occlusion are all symptoms of sickle cell disease (a hemoglobinopathy) that reduce both life wellbeing and quality of life. Oxidative stress is more prevalent in patients with sickle cell disease and has been linked to hemolysis, vasoocclusion, and organ loss. ROS or their metabolites may serve as targets for antioxidant treatment or as disease severity indicators.

Keywords: Sickle cell disease, Role, Hemolytic Rate, Sources

1. INTRODUCTION

Persistent hemolyticanemia, intermittent vaso-occlusive episodes& an enhanced propensity to infection characterise sickle cell disease [1,2]. Sickle cells, protein, PMNs, & inflammatory mediators all contribute to the chronic activation & death of endothelial cells, causing progressive microvascular damage in a number of organs [3-6]. Microvascular dysfunction, vaso-occlusion& organ destruction are all symptoms of sickle cell disease, and increased oxidative stress may play a substantial role in the development of these complications [7]. Increased intravascular hemolysis, ischemia-reperfusion damage, as well as chronic inflammation [8-10] contribute to the high rate of ROS formation in sickle cell disease.

In order to generate ROS, intracellular catabolism requires oxygen just as an electrophile (oxidant). Intermediate ROS were formed during this process even in healthy people [11, 12], including superoxide (O2), H_2O_2, and hydroxyl radicals (OH). The antioxidativedefense system (dismutase, catalase, gluthatione& chondroitin oxidase, ascorbate, glycolysis, flavonoids, &

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carotenoids) and low levels of ROS protect or reduce oxidative damage under normal conditions [13].One of the primary causes of oxidative stress is a deficiency in antioxidants and an abundance of oxidants.Damage to lipids, proteins, &DNA from oxidative reactions is what ultimately leads to (premature) cell death when oxidant production is elevated and/or antioxidant defences are compromised.

Persistent oxidative stress is a hallmark of SCD [14]. Here, we take a look at oxidative stress of SCD, its mechanisms, the part reactive oxygen species play in the development of the disease, and their potential as diagnostic indicators and therapeutic targets.

Some of the most important prooxidant sources for sickle cell disease come from the erythrocytes themselves, where the combination of unstable autoxidativeHbS and enhanced metabolic turnover due to repeated HbS polymerizations &depolymerizations leads to enhanced ROS formation [15]. Sickle erythrocytes have a faster metabolic turnover throughout polymerization &depolymerization, which causes them to produce more reactive oxygen species (ROS) [16]. Two times as much O_2, H_2O_2, hydroxyl radical (HO•), or lipid oxidation products are generated by sickle erythrocytes as by HbA-containing erythrocytes [20,21]. Since SCD is characterised by elevated and sustained prooxidant production, the disease is also associated with an antioxidant insufficiency due to excessive consumption of antioxidants. Some research on SCD have found an increase in RBC-SOD activity [18], [19], with authors theorising that this is a defensive measure in response to a rise in oxidative that may contribute to H2O2 accumulation. However, other investigations have found a decrease in SOD activity [22,23]. In addition, the severity of SCD is correlated with a patient's RBC-SOD level, which is less in people with SCD than it is in healthy participants.

Two important antioxidant enzymes, GPx and CAT, eliminate H2O2 [24]. Two-electron transfer and sickling can both generate H2O2. Energy-efficient H2O2 removal occurs via CAT rather than GPx because CAT may breakdown H2O2 without using up cell reducing equivalent (GSH or NADPH) [25]. Using transgenesis sickle mice models [56] or in SCD patients [26], some researchers have found decreased CAT activity; however, other researchers have not found this to be the case.In contrast, a study[27] reported that CAT levels were higher in SCD patients. Decreased CAT levels may arise from prolonged & severe oxidative stress [28,29], while elevated CAT levels maybe serving as a safe mechanism to scavenge H_2O_2.There's also the idea that the enlarged reticulocytes seen in sickle cell disease patients' blood are to blame for the abnormally high quantities of antioxidant enzymes seen in their erythrocytes.

- **Oxidative stress in sickle cell disease: sources**

  Sickle cell illness is associated with a significant oxidative burden because of the elevated quantities of cell-free haemoglobin & the catalytic activity it displays in oxidative processes.Four, sickle haemoglobin oxidation is boosted (HbS).

a. Cell-free hemoglobin: To prevent cell damage, iron homeostasis is tightly regulated under physiological conditions by a variety of complicated systems [30]. Sickle cell patients have significantly higher quantities of cell-free haemoglobin in their plasma compared to healthy

individuals [31]. Cell-free ferrous haemoglobin blocks NO's vasodilatory, antithrombotic, and anti-inflammatory activities [32]. Endothelial cells produce iron by synthesising the hydrophobic heme, that intercalates rapidly into to the cell membrane [33]. As a result, endothelial cells become activated and injured due to an increase in the nonenzymatic generation of ROS.Multiple investigations [34] support the hypothesis that an increase in endothelial ROS generation as a result of bleeding is responsible for the negative relationship between hemolytic frequency in SCD and endothelial activity. Patients with sickle cell disease, who experience persistent intravascular hemolysis, have abnormally low amounts of a cell-free haemoglobin scavenger haptoglobin [35]. Endothelial cells upregulateheme oxygenase-1 or ferritin in response to heme-induced oxidative stress, providing some protection against iron toxicity [36].

b. **Ischemia-reperfusion:** Reperfusion injury occurs when oxygen-rich blood flow is restored after ischemia; this process exacerbates tissue damage, which is mediated by oxidants produced during reperfusion. Low oxygen tension stimulates the formation of hypoxanthine and xanthine oxidase from adenosine triphosphate and xanthine dehydrogenase, respectively, in the absence of blood flow[37]. Following the restoration of oxygen-rich blood flow, xanthine oxidase produces superoxide during the reduction of xanthine or hypoxanthine to uric acid. Iron catalyzes the transition of the superoxide radical into the highly damaging and extremely potent hydroxyl radical that is reactive with practically all biological molecules. NADPH oxidase, which is prevalent in PMNs and monocytes, is important for oxidative damage in the latter phase of reperfusion injury [37]. Significant amounts of xantine oxidase are released into the circulation following ischemia-reperfusion injury, especially to hepatocellular tissue, which, after diffusing to the endothelium, increases vascular ROS generation and NO scavenging, resulting in impaired vascular function in sickle cell disease.

c. **Inflammation and oxidative stress:** The formation of ROS is a hallmark of inflammation & has been linked to numerous chronic inflammatory diseases. In addition to helping kill off microorganisms, ROS also have a role in activating inflammatory mediators, triggering the production of integrins, and damaging endothelial cells. Patients with sickle cell disease exhibit a pro-inflammatory state that persists despite the absence of any symptoms. Higher levels on oxidative indicators, such as F2-isoprostanes, are observed in sickle cell disease patients. Inflammation caused by SCD may generate ROS, and the increasing amount of activated PMNs could be a source of these ROS. In sickle cell patients, PMNs produce ROS during a NADPH oxidase-mediated respiratory surge that is constantly active [38]. Despite the potential bidirectional nature of the connection, it is unclear whether oxidative stress contributes to the prolonged pro-inflammatory state associated with SCD or vice versa. Heme, when present in the blood at levels seen in heterozygous sickle cell disease patients, promotes the expression on proinflammatoryintegrins on endothelium or blood cells, raises vascular permeability, increases leukocyte inflow, and enhances reactive oxygen species (ROS) formation.

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d. Autoxidation of HbS: Methemoglobin construction in HbS was 1.7 times quicker than in normal HbA [39], although the most updated research by the same group suggests that this estimate is inflated, illustrating that HbS only had a slightly higher oxidation rate [20], that could be due to an oxidatively stressed cytoplasmic environment as opposed to unstable HbS. The high metabolic cycle that occurs during polymerization as well as depolymerization after deoxygenation and reoxygenation, correspondingly, may be a major source of ROS production [40].

2. LITERATURE REVIEW

Nancy J. et.al. (2015) [41] investigated SCD is characterized by rigid red blood cells in both people and mice (RBCs). Docosahexanoic acid (DHA), an omega-3 fatty acid, may influence RBC deformability through membrane integration. In this study, sickle cell disease (SS) mice were fed either a control diet with the same total fat content or natural component rodent meals enriched with 3% DHA (CTRL diet). We examined the RBCs' stiffness using atomic force microscopy and deformability in ektacytometry, or percentage of permanently sickled RBCs on smears of peripheral blood after eight weeks of feeding. Atomic force microscopy revealed that compared to RBCs from wild-type mice, those of SS mice fed a CTRL diet were less flexible and more rigid. RBCs of SS mice fed a DHA diet were much less stiff and more malleable than RBCs in SS mice on the CTRL diet.

Erica N. et.al. (2015) [42] examined Hemoglobinopathy, that Most common genetic disorder worldwide, and that does include sickle cell disease. Despite the fact that the polymerization of red blood cells during their deoxygenating phase is the initial cause of sickle cell disease complications, it has been shown that oxidative stress brought about by the biological processes of the disease affects the pathophysiology of sickle cell disease. It is well known that healthy people who exercise regularly experience less oxidative stress, and that this is due in large part to enhance in the effectiveness of antioxidant enzymes. In addition, recent studies on sickle cell disease & other disorders, sickle cell trait carrier, or a mouse model of the ailment have revealed that regular exercise can reduce oxidative stress.

Silva et.al. (2013) [43] proposed that Hemoglobin (Hb) adds a substantial quantitative source to biological systems' ability to synthesise superoxide (O2•), erythrocytes have a continuous environment of prooxidant production. In order to prevent themselves from being damaged by free radicals, erythrocytes have an antioxidant defence system built in. Aside from providing antioxidant protection themselves and other tissue and organs, red blood cells (RBCs) are also able to preserve haemoglobin (Hb) through a selective barrier that allows the passage for gaseous & other ligands. Polymerization or thermal decomposition of HbS molecules generates ROS that can set off a chain reaction that includes, among other things, blood cell adhesion, hemolyticanemia, vasoocclusion, or ischemia-reperfusion damage. Sickle cell anaemia, in other words, is associated with a pathophysiologic condition characterised by chronic & systemic oxidative stress due to a number of prooxidant causes.

Nur, E. et.al. (2011) [44] examined that Hemolyticanemia, enhanced susceptibility to infections, as well as vaso-occlusion were all symptoms of the hemoglobinopathy known as sickle cell

disease (SCD), It decreased not only longevity but also quality of life. Patients with sickle cell disease are more likely to experience oxidative stress, which has been linked to hemolysis, vaso-occlusion, & organ death.Additionally, further study is necessary to determine whether antioxidants and medications with antioxidative effects can help sickle cell patients postpone or avoid the development of organ disorders.

3. SICKLE CELL DISEASE SYMPTOMS IN CHILDREN

Symptoms of SCD often appear within the first 5 months of life, with the majority of cases diagnosed by the end of the first year. The severity of symptoms in individual children varies. They could be relatively minor or quite severe. There may be a variety of symptoms, such as:

- **Anemia:** This is the most prevalent symptom. Red blood cell deficiency is the source of anemia. A child with anemia could appear pale and weary.
- **Yellowing of the skin, eyes, and mouth (jaundice):** This is a common symptom. Red blood cells have a shorter lifespan than sickle cells. They expire before the liver can remove them. When red blood cells die, they emit bilirubin, the substance responsible for the yellow color.
- **Pain crisis, or sickle crisis:** When moving via narrow blood arteries, sickle cells might become stuck. This causes discomfort by cutting off blood flow. Any part of the body is susceptible to this kind of excruciating pain, but the chest, arms, and legs are most vulnerable. Finger & toe swelling in newborns and young children can be painful. Tissue death may also result from a reduction in blood supply.
- **Acute chest syndrome:** This occurs when sickle cells cluster together in the lungs' minute blood capillaries and block oxygen passage. It's possible that this will end in tragedy. When the brain is under duress from an infection, illness, or fluid loss, this condition often appears abruptly (dehydration). Symptoms may include heat, discomfort, and a hacking cough.
- **Splenic sequestration (pooling):** When sickle cells become trapped and accumulate in the spleen, it swells and becomes painful. Red blood cell mobility decreases. This can result in a rapid hemoglobin decrease. It can be fatal if not treated immediately.

4. ROLE OF SICKLE CELL DISEASE IN CHILDREN

A single base mutation in the -globin gene results in the production of sickle HbS, a form disease hemoglobinopathy that is closely related with hereditary hemolytic anaemia [45]. Manifestation of SCD as a phenotype is a complex pathophysiologic state combining several pro-oxidant processes and, as a result, not just chronic but it also systemic peroxidation.Erythrocytes in normal biological systems are constantly surrounded by free radical production. On the other hand, ROS or its oxidation products are possible SCD severity markers [46]. However, the constant polymerization or depolymerization of HbS molecules generates an increasing amount of ROS, This can set off a chain reaction leading to microvascular injury in organs and blood

vessel adhesion, hemolysis, and an elevated risk of infection and inflammatory illness, thereby reducing life wellbeing and quality of life [47,48].

Sickle erythrocytes are the principal source of pro-oxidants in sickle cell disease patients because of the accelerated metabolic turnover caused by the recurrent HbS polymerizations/depolymerizations and the instability of autoxidativeHbS [29,50]. Superoxide ($O2•^{-}$), H_2O_2, HO•, or lipid oxidation products are produced by sickle erythrocytes at twice the rates of those produced by HbA-containing erythrocytes, according to a number of studies [51]. In the presence of hydrogen peroxide & transitional as well as redox-active metal ions, including such iron or copper, O2• was converted to a highly reactive HO• via the Fenton or Haber-Weiss reactions [10].Therefore, it was hypothesised that the release of iron after RBC hemolysis contributed significantly to the increased ROS production among SCD patients. Antioxidants such as vitamins and the enzymes SOD, CAT &GSH are found in erythrocytes [51]. Changes in RBC membrane characteristics, membrane permeability, or hemolysis result from an excess of ROS, which overwhelms the blood's defences and damages biological macromolecules like proteins, lipids, and DNA [52]. Sickle erythrocytes have such a higher endogenous content of oxidised lipid and are more susceptible to subsequent lipid peroxidation (LPO) [53] compared to HbA-containing erythrocytes. Patients with SCD often experience a chronic inflammatory process characterised by, among other things, endothelial dysfunction, increased production of free radicals hemolyticanemia, expression levels of integrins other than leukocytes, stimuli of granulocytes, monocytes, and also platelets, or an increased supply of proinflammatory.

Globally, the hematological profiles of SCD patients of varying ages and geographical areas are extraordinarily varied. In addition, neonatal and early childhood anemia is prevalent [54]. There is a lack of information about the haematological profile and challenges of children with SCD. In addition, the pathophysiology of SCD in children and the potential utility of oxidative stress as a biomarker for the disease have not been the subject of extensive study.The purpose of this research was to determine whether or not antioxidants could counteract the effects of high quantities of radical oxygen/nitrogen species, as well as the damage to biomolecules including protein, lipid, and DNA in children with SCD.In addition, the levels of inflammatory mediators in the plasma of SCD youngsters were evaluated.

RESEARCH METHODOLOGY

Prospective case-control studies were undertaken at the Central Study Center at Cairo, Egypt, or the New Children's Hospital at the Child Medical and Health Biochemistry Departments of India. Following consent from parents, the experiment included 40 kids with confirmed homozygous (HbSS) SCA diagnosis (24 boys & 16 girls, mean age 10.6 4.5 years) & 20 age- & sex controls (12 boys & 8 girls, mean age 10.0 2.8 years [$p > 0.05$]). Everyone who took part in the study was in stable health and received the standard afterwards (from December 1, 2011 to June 30, 2012). Patients over the age of 18, those with a history of acute VOC or acute febrile sickness within the previous three months, those with comorbid serious disease, and those who were already part of a routine blood donation programme were not allowed to participate. All of the recruits were devoid of vitamin E and other antioxidants. The 18th Medical Library Congress

of India gave their stamp of approval after the study's protocol was approved by the "Ethics Committee of the National Study Center" in India in accordance with the rules established by the Institutional Review Board again for Safety of Human Subjects.

Thorough clinical evaluations and exhaustive history taking were carried out. As a clear definition, an VOC was anything besides hand-foot sickness, breast syndrome, septic arthritis, and any event of harm that could be completely cured at home that caused pain inside the limbs, back, belly, shoulders, and head that required hospitalisation and weren't characterised by SCD.At enrolment, participants reported the total number of times they had had severe pain and over previous 12 months (frequency of VOC per year). Mean daily hydroxyurea (HU) dose for 31 patients was 19.8 3.4 mg/kg (range 15-30 mg/kg, once-day oral administration). A HU might expect to live for about 2.12 1.49 years on average. No attempt was made to attain the maximum tolerated dosage (MTD) during dose escalation, and three patients were already at the MTD when they participated.

As shown below, blood samples were taken and analysed for levels of MDA, nitrite, PON, TAO, and vitamin E. Blood was drawn in a volume of 5 ml & allowed to clot at 25 C for 30 min; the blood then was centrifuged at three thousand revolutions per minute (rpm) at four degrees Celsius, and the serum was collected in clean, labelled tubes for further study.

Determination of lipid peroxidation: Levels of malondialdehyde (MDA) were used as a proxy for lipid peroxidation. Chemicals that react to thiobarbituric acid result in a compound with peak absorption at 532 nm as well as a red colour using the method described by Ruiz-Larreaet al.17.

Determination of serum nitrite: The Griess reagent method18 was used to quantify blood nitrite (NO2-), an adequate surrogate indication for serum NO. The NO radical produces nitrite, which is then used as a signal to initiate the production of more NO radicals.

Determination of PON activity: Determination of PON's arylesterase activity in phenylacetate-containing supernatants using spectrophotometry.

Measurement of serum TAO levels: Automated measurement based on bleaching the characteristic colour of a more absorbent material was used to determine serum TAO concentrations. Antioxidants' effects on the 2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) radical are listed in Table 2. Antioxidants' concentrations and antioxidant capacities determine whether or not the ABTS radical cation is decolored. The data is presented as mmolTrolox EL/L.

Table 2: Malondialdehyde, nitrite, paraoxonase, total antioxidant capacity, as well as vitamin E levels in sickle cell anemia patients receiving HU and those not getting HU were compared

Variables	**SCA cases receiving HU (n = 32)**		**SCA cases not receiving HU (n = 10)**		**p-value**
	Mean ± SD	**Range**	**Mean ± SD**	**Range**	

MDA (nmol/mL)	2.56 ± 0.33	2-3.5	2.59 ± 0.35	2.1-3.3	0.92
Nitrite (um/mL)	8.65 ± 0.92	6.7-10.3	8.40 ± 1.55	6.9-11.9	0.50
PON (u/mL)	186.8 ± 30.7	109-243	207.5 ± 37.7	149-270	0.12
TAO (mmol/L)	0.89 ± 0.11	0.64-0.11	0.83 ± 0.11	0.57-0.94	0.10
Vitamin E (mg/mL)	0.19 ± 0.128	0.007-0.6	0.3 ± 0.13	0.01-0.5	0.588

MDA: malondialdehyde

HU: hydroxyurea

PON: paraoxonase

SCA: sickle cell anemia

SD: standard deviation

TAO: total antioxidant capacity

Measurement of vitamin E: The HPLC analysis of tocopherol (vitamin E) was successful. Newly obtained erythrocytes were kept in ethanol with 2% pyrogallol at -70 degrees Celsius. Within a month of collection, each sample was analysed with a UV/VIS detector at 292 nm and a solvent solution containing 95% methanol and a reverse-phase C-18 column.

6. STATISTICAL ANALYSIS

Patients' information was analysed using SPSS for Windows, version 17.0. We utilised the Mann-Whitney U testing and the Student's t-test on independent samples to compare continuous variables. The quantitative variables are correlated utilizing Whitney's Spearman’s rank order test.The chi-square test is useful for comparing groups based on qualitative factors expressed as numbers (frequency, percentage). Reliability, sensitivity, validity, PPV, and NPV were evaluated with a logistic regression analysis. Area under the curve (AUC) and receiver operating characteristic (ROC) were computed. The optimal cutoff points for all required variables have been identified. A p-value less than 0.05 was considered significant.

7. RESULTS

Analysis of the differences between SCA patients and controls with respect to the assessed parameters. SCA patients showed significantly greater levels of MDA and significantly lower amounts of nitrite, PON, TAO& vitamin E compared to a control group. This gender-based

disparity was also found for all other studied variables, both in both patients and controls with the same gender. Average levels of nitrite, peroxynitrite, thioacetaldehyde, and malondialdehyde in SCD patients showed no significant variations between the sexes.

The amounts of MDA, vitamin E, para-oxoanthracenal, and thioacetoxyol (TAO) were not correlated with the frequency for volatile organic compounds ($p > 0.05$). Meanwhile, serum nitrite was inversely linked with the presence of volatile organic compounds ($r = -0.3$, $p = 0.04$), and not with haemoglobin, malondialdehyde, paraoxonase, or tocopherol ($r = 0.20$, -0.5, 0.09, 0.02& 0.05, respectively, $p > 0.05$). There was no association between PON, TAO, or vitamin E and MDA ($p > 0.05$).

Table 3: Correlations between PON levels and clinical and laboratory parameters of Child patients

	r-coefficient	**p-value**
Age (years)	0.26	0.17
Age at diagnosis (years)	0.32	0.08
VOC frequency (times/year)	-0.23	0.21
Weight (kg)	0.406	0.009 a
BMI (kg/m^2)	0.68	< 0.002 a
Hemoglobin(g/dL)	0.18	0.33
Reticulocyte (%)	-0.059	0.725
LDH (U/L)	0.249	0.128
MDA (nmol/mL)	-0.23	0.12
Nitrite (um/mL)	0.09	0.64
TAO (mmol/L)	-0.138	0.406
Vitamin E (mg/mL)	-0.09	0.63

BMI: body mass index

LDH: lactate dehydrogenase

MDA: malondialdehyde

PON: paraoxonase

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TAO:total antioxidant capacity

VOC:vaso-occlusive crises.

a: Statistically significant values

Nitrite, peroxynitrite, and trichloroaniline (TAO) were tested for their ability to detect volatile organic compounds at varying threshold concentrations. Nitrite, PON, or TAO were compared using the ROC curve since there is no standard method. Overall, nitrite is more reliable than PON and TAO, as indicated by the AUC of 0.782 for nitrite versus 0.701 and 0.650, respectively ($p = 0.006$). Nitrite was once a reliable predictor for volatile organic compounds (VOC), but it lost either its sensitivity or specificity when the parameters were adjusted.

Nitric oxide (NO) or HO• generation in the plasma of children with SCD was higher than that of healthy children. SOD, CAT, GSH, GPx, and protein thiol all had significantly decreased plasma levels in SCD children. At different ages, children with SCD showed markedly different levels of indicators for plasma oxidative stress, protein carbonylation, and DNA damage.Persistent changes in haemoglobin concentration, erythrocytes, serum bilirubin, platelet, creatinine, leukocytes, as well as the expression major inflammatory mediators were also observed in children with SCD, suggesting that they suffered from a chronic inflammatory condition.

CONCLUSION

According to the outcomes of the current investigation, oxidative stress occurs in SCA patients less than 18 years old.This highlights the importance of conducting clinical trials to establish whether or not providing these children with vitamin E or other drugs that raise their overall antioxidant potential can improve their clinical course. Elevated levels of volatile organic compounds (VOCs) may develop as a result of long-term exposure to oxidative stress in children with SCA. Children with SCA may have an increase in the frequency of VOCs alongside a drop in serum nitrite. Our study's unexpected observation that PON levels drop in SCA patients offers a viable avenue for further research.

Due to an increase in the formation of ROS, oxidative processes in SCD cause damage to various types of cells including erythrocytes or endothelium. Consistently elevated concentrations of oxidative stress have been linked to the development of organ damage in SCD.SCD disease severity may be measured by oxidative stress secondary metabolites. Extensive research is warranted into the possibility that antioxidants and antioxidative medicines can prevent or delay the onset of organ failure in sickle cell patients. Further research on oxidation and inflammation in SCD patients is required to direct adjuvant therapy decisions, and the inflammatory profiles of children with SCD appears to be closely related with oxidative stress. Unfortunately, neither the molecular pathways triggered by erythrocytes nor their role in the generation of free radicals have been thoroughly investigated& neither have the inflammatory responses or oxidative stresses experienced by children with SCD. Therefore, it is crucial and potentially fruitful to pursue additional research into oxidative stress biomarkers or anti-oxidant therapeutic techniques that reduce the body's production of oxidative stress and get rid of any lingering inflammation.

Therapeutic drugs to reduce oxidative stress inside sickle erythrocytes and alleviate the condition may be developed with the help of identifying signs of oxidative stress and implementing antioxidant therapy approaches.

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