

ORIGINAL ARTICLE

OXIDATIVE STRESS BURDEN IN PAEDIATRIC SICKLE CELL ANAEMIA: EFFECTS OF HYDROXYUREA THERAPY, DISEASE SEVERITY, AND SOCIOECONOMIC FACTORS

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ABSTRACT

Background: Oxidative stress plays a central role in the pathophysiology of sickle cell anaemia (SCA), contributing to haemolysis, endothelial dysfunction, and disease complications. Hydroxyurea (HU), the main disease-modifying therapy for SCA, may influence oxidative balance; however, evidence in children from resource-limited settings remains limited.

Objective: To evaluate oxidative stress and antioxidant status among children with sickle cell anaemia, comparing hydroxyurea users and non-users, and to examine variations according to clinical disease severity and socioeconomic status.

Methods: This cross-sectional comparative study included 110 children with SCA aged 2–17 years attending Wesley Guild Hospital, Ilesa (WGH). Participants were stratified into HU users ($n = 55$) and non-HU users ($n = 55$). Oxidative stress markers, enzymatic and non-enzymatic antioxidants, and antioxidant vitamins were measured using Waters' high performance liquid chromatography methods. Disease severity was assessed using the Kuti and Adegoke severity scale, while socioeconomic status was classified using the Olusanya socioeconomic classification. Data was analyzed using appropriate parametric tests, with statistical significance set at $p < 0.05$.

Results: Hydroxyurea users had significantly lower white blood cell counts compared with non-users ($p = 0.018$). Although mean malondialdehyde level was lower in HU users, the difference was not statistically significant ($p = 0.181$). No significant differences were observed in other oxidative stress markers, antioxidant enzymes, antioxidant vitamins, or total antioxidant capacity between HU users and non-users. Oxidative and antioxidant parameters did not differ significantly across disease severity categories or socioeconomic classes.

Conclusion: Children with sickle cell anaemia exhibit a persistent oxidative burden irrespective of hydroxyurea use, disease severity, or socioeconomic status. While hydroxyurea demonstrates favourable haematological effects, its impact on oxidative stress appears limited. Adjunctive strategies targeting oxidative stress may be necessary to improve clinical outcomes in paediatric SCA.

Introduction

Sickle cell anaemia (SCA) is one of the most common inherited haemoglobin disorders worldwide and remains a major cause of childhood morbidity and mortality, particularly in sub-Saharan Africa.^{1–3} The disease is characterised by chronic haemolysis, recurrent vaso-occlusive episodes, and progressive multi-organ damage, driven by complex interactions between erythrocyte sickling, inflammation, endothelial dysfunction, and oxidative stress.^{4–6} Despite advances in disease-modifying therapy, oxidative injury continues to play a central role in the pathophysiology and clinical heterogeneity of SCA.^{7–9}

Oxidative stress in SCA arises from an imbalance between excessive production of reactive oxygen species (ROS) and inadequate antioxidant defence. Repeated cycles of haemoglobin polymerisation and depolymerisation, increased auto-oxidation of sickle haemoglobin, chronic inflammation, and ischemia-reperfusion injury contribute to sustained ROS generation. Elevated levels of lipid peroxidation products, such as malondialdehyde (MDA), alongside depletion or dysregulation of antioxidant enzymes and vitamins, have been consistently reported in both children and adults with SCA. This redox imbalance promotes membrane damage, exacerbates haemolysis, impairs nitric oxide bioavailability, and contributes to endothelial activation and vaso-occlusion.^{10–11}

Hydroxyurea (HU) is currently the most widely used disease-modifying therapy for SCA and has been shown to reduce pain episodes, transfusion requirements, and mortality. Its primary mechanism of action

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involves induction of fetal haemoglobin (HbF), which reduces erythrocyte sickling.¹² In addition, HU exerts pleiotropic effects, including reduction of leukocytosis, improvement of red cell hydration, modulation of nitric oxide metabolism, and attenuation of inflammation.¹³ Emerging evidence suggests that HU may also influence oxidative stress pathways;^{13,14} however, findings remain inconsistent, particularly in paediatric populations and resource-limited settings.^{15–17}

The burden of oxidative stress in SCA may also be influenced by clinical disease severity and socioeconomic factors. Patients with more severe phenotypes are thought to experience higher oxidative injury due to increased haemolysis, inflammation, and frequency of vaso-occlusive crises.¹⁷ Similarly, lower socioeconomic status may exacerbate oxidative stress through poor nutrition, recurrent infections, and limited access to comprehensive care.¹⁸ However, data examining the interplay between oxidative stress, disease severity, socioeconomic status, and hydroxyurea use are sparse, especially in African settings where the disease burden is highest.

In Nigeria and other sub-Saharan African countries, where most children with SCA reside, access to hydroxyurea remains variable,¹⁵ and the role of oxidative stress as a potential therapeutic target is not fully characterized. Understanding the oxidative and antioxidant profiles of children with SCA in this context is critical for identifying gaps in care and informing adjunctive treatment strategies.

Therefore, this study aimed to evaluate oxidative stress and antioxidant status among children with sickle cell anaemia, comparing hydroxyurea users and non-users, and examining variations according to clinical disease severity and socioeconomic class. By providing a comprehensive assessment of enzymatic and non-enzymatic antioxidant systems alongside established oxidative stress markers, this study seeks to clarify the extent to which hydroxyurea use and clinical factors modulate oxidative balance in paediatric SCA.

Methods

Study Design and Participants

This cross sectional analysis included 110 children with sickle cell anaemia (SCA) attending routine follow up at Wesley Guild Hospital, Ilesa, Southwestern Nigeria. All study participants were in steady state; and those on HU therapy (irrespective of dosage, dosage range from 7 – 23 mg/kg/day) for at least 6 months were recruited as HU users, while the comparison group were HU naive. Only children with SCA (HbSS) were recruited for this study because they were the predominant SCD children on HU.

Sociodemographic information, including age, sex, parental education, and occupation, was obtained using structured questionnaires. Clinical data, including hydroxyurea use, dose and duration of use were extracted from medical records. Socioeconomic class was determined using the Olusanya classification.¹⁹ Disease severity was categorized using the Adegoke & Kuti clinical severity score that utilized both clinical and blood parameters to classify children with SCA into mild, moderate and severe.²⁰

Biochemical Measurements

Blood samples were obtained from all participants for the quantification of plasma malondialdehyde (MDA), hydrogen peroxide (H₂O₂), which are markers of oxidative stress, superoxide dismutase (SOD), catalase, nitric oxide (NO), flavonoids, carotenes, and vitamins which are enzymatic and non-enzymatic antioxidants. Complete blood count was done for all study participants. Markers of oxidative stress and antioxidants were analyzed using Waters' high performance liquid chromatography (HPLC). Packed cell volume (PCV), white blood counts (WBC) and platelets count were determined using auto-analyzer.

Statistical Analysis

Descriptive statistics were reported as means $\pm$ standard deviations (SD) or frequencies and percentages. Independent samples t tests compared means of plasma oxidants and antioxidants between HU users and non users. ANOVA compared means of oxidants and antioxidants across socioeconomic classes. Statistical significance was set at $p < 0.05$.

Results

Participant Characteristics

A total of 110 children with sickle cell anaemia were included in the study. The mean age of participants was 9.3 ± 3.2 years, with an almost balanced sex distribution (50.9% male, 49.1% female). Fifty-five (50%) were on hydroxyurea (HU) therapy, while the remaining 55 (50%) were not. The average duration of HU use was 15.2 ± 6.8 months. Socioeconomic status was classified using the Olusanya classification, with 16 (14.5%) participants in the upper class, 76 (69.1%) in the middle class, and 18 (16.4%) in the lower class. Disease severity was assessed using the Adegoke and Kuti severity score, with 93 (84.5%) participants classified as mild and 17 (15.5%) as moderate/severe. Table 1 shows participants' characteristics.

Table 1. Sociodemographic and Clinical Characteristics of Study Participants.

Character-istics	Total (n=110)	HU Users (n = 55)	Non HU Users (n = 55)	p-Value
Age, mean ± SD (years)	9.3 ± 3.2	9.5 ± 3.7	9.4 ± 3.6	0.903
Gender				
Male, n (%)	56 (50.9)	28 (50.9)	28 (50.9)	1.000
Female, n (%)	54 (49.1)	27(49.1)	27 (50.9)	
Disease Severity				
Disease severity mild, n (%)	93 (84.5)	47 (85)	46 (84)	0.184
moderate/ severe, n (%)	17 (15.5)	8 (15)	9 (16)	
Socioeconomic class				
Upper, n (%)	13 (23.6)	3 (3.3)	16 (14.5)	0.006*
Middle, n (%)	31 (56.4)	45 (81.8)	76 (69.1)	
Lower, n (%)	11 (20.0)	7 (12.7)	18 (16.4)	

HU = hydroxyurea; SD = standard deviation; n = number; *statistically significant.

Comparison of Oxidative and Antioxidant Status Between Hydroxyurea Users and Non-Users

A total of 110 children with sickle cell anaemia (SCA) were enrolled, comprising 55 hydroxyurea (HU) users and 55 non-HU users. There was no statistically significant difference in haematocrit between HU users and non-users ($23.73 \pm 3.81\%$ vs $23.31 \pm 4.03\%$; $p = 0.571$). However, mean white blood cell (WBC) count was significantly lower among HU users compared with non-HU users ($11,703.64 \pm 3,909.91$ cells/mm³ vs $13,945.45 \pm 5,714.20$ cells/mm³; $p = 0.018$).

Markers of oxidative stress and antioxidant defence showed no statistically significant differences between HU users and non-users. Mean malondialdehyde (MDA) levels were lower among HU users compared with non-HU users (3.83 ± 1.53 ng/dl vs 4.19 ± 1.31 ng/dl), although this difference did not reach statistical significance ($p = 0.181$). Similarly, hydrogen peroxide, superoxide dismutase (SOD), glutathione peroxidase, glutathione transferase, total glutathione, nitric oxide, catalase, and total antioxidant capacity (TAC) were comparable between the two groups (all $p > 0.05$).

Antioxidant vitamin levels (vitamins A, C, D, and E), β -carotene, flavonoids, lipid peroxidation indices, and glutathione-S-transferase activity also did not differ significantly between HU users and non-users (Table 2).

Table 2: table showing oxidant status among HU users and non-HU users

Category	HU users, n = 55 (mean $\pm$ SD)	Non HU users, n = 55 (mean $\pm$ SD)	p-value
Parameters			
Hct (%)	23.73 $\pm$ 3.81	23.31 $\pm$ 4.03	0.571
WBC (cells/mm ³)	11703.64 $\pm$ 3909.91	13945.45 $\pm$ 5714.20	0.018
MDA (ng/dl)	3.83 $\pm$ 1.53	4.19 $\pm$ 1.31	0.181
H ₂ O ₂ (ng/dl)	4.22819 $\pm$ 0.67	4.30 $\pm$.80	0.579
SOD (ng/dl)	1.01 $\pm$ 0.23	1.07 $\pm$ 0.21	0.152
Glutathione peroxidase (ng/dl)	2.48 $\pm$ 0.39	2.58 $\pm$ 0.35	0.198
Glutathione transferase (ng/dl)	7.79 $\pm$ 1.77	8.05 $\pm$ 1.87	0.456
Glutathione (ng/dl)	8.32 $\pm$ 1.89	8.74 $\pm$ 1.66	0.219
Nitric oxide (ng/dl)	8.91 $\pm$ 2.03	9.21 $\pm$ 2.14	0.458
Catalase (ng/dl)	6.93 $\pm$ 1.58	7.17 $\pm$ 1.66	0.453
Vitamin A (ng/dl)	10.61 $\pm$ 2.42	10.97 $\pm$ 2.51	0.440
Vitamin C (ng/dl)	7.94 $\pm$ 2.42	7.40 $\pm$ 2.62	0.266

Vitamin E (ng/dl)	1.33 $\pm$ 0.40	1.28 $\pm$ 0.48	0.555
Vitamin D (ng/dl)	2.96 $\pm$ 0.90	2.88 $\pm$ 0.99	0.654
TAC (ng/dl)	0.33 $\pm$ 0.10	0.32 $\pm$ 0.12	0.763
TCarotene (ng/dl)	4.76 $\pm$ 1.45	4.43 $\pm$ 1.61	0.258
Flavinoid (ng/dl)	6.42 $\pm$ 1.46	6.75 $\pm$ 1.28	0.219
MDA_lip_per (ng/dl)	2.70 $\pm$ 0.61	2.84 $\pm$ 0.54	0.219
GST_glut_Trif (ng/dl)	5.41 $\pm$ 1.23	5.68 $\pm$ 1.08	0.219

H₂O₂ – Hydrogen peroxide; MDA – Malondialdehyde; SOD – Superoxide dismutase; WBC- White blood cell; Hct- Haematocrit, TAC- Total antioxidant capacity

Oxidative Stress Markers According to Disease Severity

When participants were stratified by disease severity using the Kuti and Adegoke severity scale, 93 (84.5%) had mild disease, 15 (13.6%) had moderate disease, and 2 (1.8%) had severe disease. Of the 93 with mild disease activity, 47 were on HU while the remaining 46 were not on HU, 6 of the 15 with moderate disease and all 2 with severe disease were on HU therapy. No statistically significant differences were observed across severity categories for any oxidative stress or antioxidant parameter.

Mean MDA levels increased modestly with disease severity (mild: 3.96 ± 1.32 ng/dl; moderate: 4.31 ± 2.08 ng/dl; severe: 4.09 ± 0.63 ng/dl), but this trend was not statistically significant ($F = 0.377$; $p = 0.687$). Enzymatic antioxidants (SOD, catalase, glutathione peroxidase) and non-enzymatic antioxidants (total glutathione, antioxidant vitamins, β -carotene, flavonoids, and TAC) were similarly distributed across severity groups (Table 3).

Although vitamin C and vitamin D levels were numerically higher in participants with severe disease, these observations were based on a very small subgroup and did not reach statistical significance.

Oxidative Stress Markers Across Socioeconomic Classes

Analysis by socioeconomic status revealed no statistically significant differences in oxidative stress or antioxidant parameters among participants from lower, middle, and upper socioeconomic classes, even though there was a statistically significant difference in socioeconomic classes between HU users and non-HU users (Table 1). Mean MDA levels were highest among participants in the lower socioeconomic class (4.28 ± 1.86 ng/dl) compared with the middle (3.94 ± 1.32 ng/dl) and upper classes (4.02 ± 1.45 ng/dl), but this difference was not statistically significant ($p = 0.663$).

Similarly, antioxidant enzyme activities, nitric oxide levels, antioxidant vitamin concentrations, TAC, lipid peroxidation markers, and glutathione-related indices were comparable across socioeconomic strata (all $p > 0.05$) (Table 4).

Table 3: Table showing means of oxidants and antioxidants of study participants across clinical severity of SCA using Kuti and Adegoke severity scale

Category	Mild n = 93 mean±SD (ng/dl)	Moderate, n = 15 mean±SD (ng/dl)	Severe, n = 2 mean±SD (ng/dl)	F	p-value
Parameters					
MDA	3.96±1.32	4.31±2.08	4.09±0.63	0.377	0.687
SOD	1.03±0.20	1.08±0.31	1.05±0.09	0.302	0.740
Glutathione peroxidase	2.52±0.34	2.61±0.54	2.55±0.16	0.382	0.684
Glutathione transferase	7.85±1.73	8.35±2.41	8.10±0.73	0.489	0.615
Glutathione	8.47±1.65	8.91±2.57	8.65±0.78	0.405	0.668
Nitric oxide	8.98±1.98	9.55±2.75	9.27±0.84	0.489	0.615
H2O2	4.23±0.72	4.44±0.91	4.34±0.28	0.484	0.617
Catalase	6.98±1.54	7.43±2.14	7.21±0.65	0.489	0.615
Vitamin A	10.69±2.33	11.37±3.28	11.03±1.00	0.488	0.615
Vitamin C	7.66±2.31	7.32±3.46	10.74±4.16	1.634	0.200
Vitamin E	1.30±0.41	1.24±0.57	1.80±0.69	1.413	0.248
Vitamin D	2.91±0.87	2.80±1.29	4.00±1.55	1.426	0.245
TAC	0.33±0.10	0.29±0.16	0.45±0.17	1.927	0.151
Tcarotene	4.62±1.35	4.19±2.29	6.44±2.50	2.006	0.139
Flavinoid	6.54±1.28	6.88±1.98	6.68±0.60	0.405	0.668
MDA_lip_per	2.75±0.53	2.90±0.83	2.81±0.25	0.404	0.668
GST_glut_tfr	5.50±1.07	5.80±1.67	5.62±0.51	0.404	0.668

H₂O₂ – Hydrogen peroxide; MDA – Malondialdehyde; SOD – Superoxide dismutase; TAC- Total antioxidant capacity.

Table 4: Table showing oxidative status from study participants across socioeconomic status

Category	Lower, n = 18 mean±SD	Middle, n = 76 mean±SD	Upper, n = 16 mean±SD	F	p-value
Parameters (ng/dl)					
MDA	4.28±1.86	3.94±1.32	4.02±1.45	0.413	0.663
SOD	1.08±0.28	1.03±0.21	1.04±0.21	0.321	0.726
Glutathione peroxidase	2.60±0.48	2.51±0.35	2.53±0.37	0.422	0.657
Glutathione transferase	8.33±2.16	7.81±1.77	8.02±1.68	0.604	0.548
Glutathione	8.89±2.31	8.44±1.66	8.56±1.79	0.453	0.637
Nitric oxide	9.52±2.47	8.93±2.03	9.17±1.92	0.605	0.548
H2O2	4.43±0.82	4.21±0.74	4.31±0.64	0.621	0.539
Catalase	7.41±1.92	6.95±1.57	7.13±1.49	0.604	0.549
Vitamin A	11.33±2.94	10.64±2.38	10.92±2.29	0.600	0.551
Vitamin C	7.22±2.08	7.66±2.64	8.18±2.42	0.610	0.545
Vitamin E	1.21±0.35	1.31±0.47	1.37±0.40	0.593	0.555
Vitamin D	2.69±0.77	2.94±0.99	3.05±0.90	0.691	0.503
TAC	0.30±0.08	0.33±0.12	0.34±0.10	0.629	0.535
Tcarotene	4.33±1.25	4.59±1.61	4.91±1.45	0.595	0.554
Flavinoid	6.86±1.78	6.52±1.28	6.61±1.38	0.453	0.637
MDA_lip_per	2.89±0.75	2.74±0.54	2.78±0.58	0.453	0.637
GST_glut_tfr	5.78±1.50	5.49±1.08	5.56±1.16	0.453	0.637

H₂O₂ – Hydrogen peroxide; MDA – Malondialdehyde; SOD – Superoxide dismutase; TAC- Total antioxidant capacity.

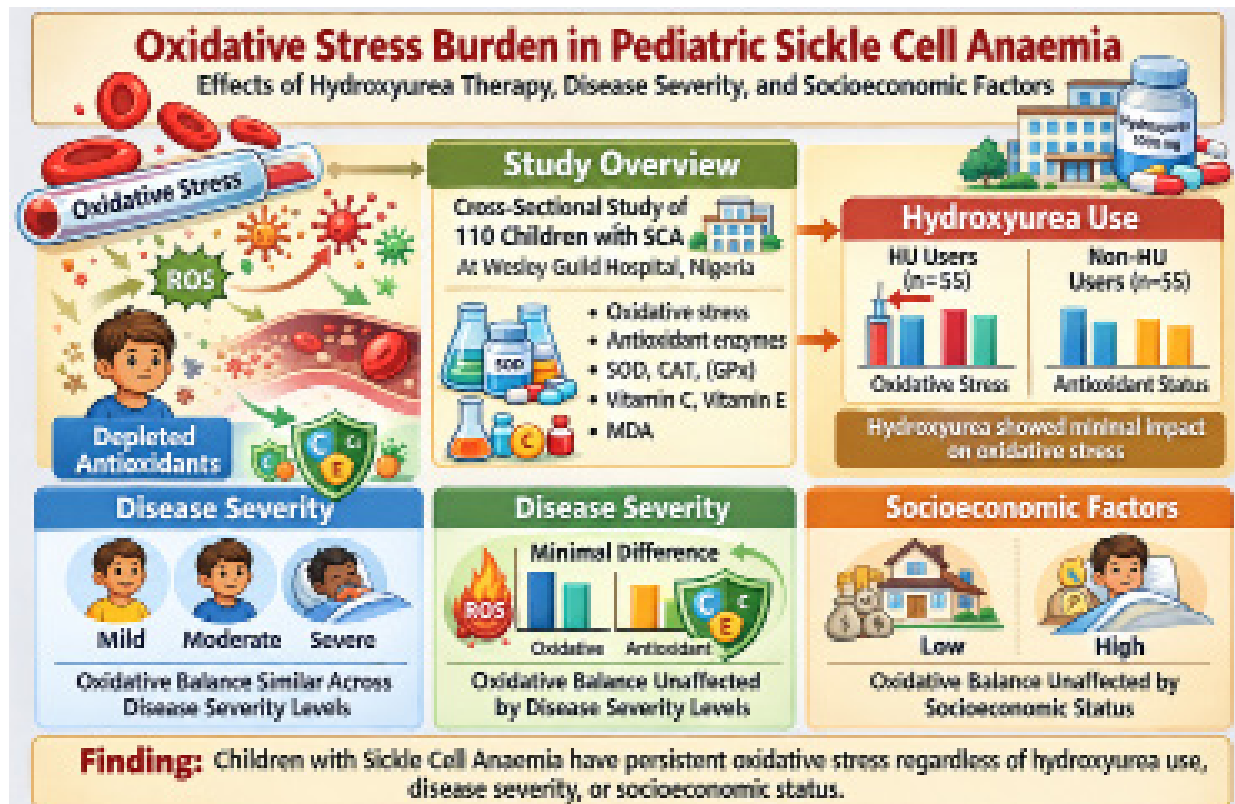
DISCUSSION

This study assessed oxidative stress and antioxidant profiles in children with sickle cell anaemia in relation to hydroxyurea use, clinical disease severity, and socioeconomic status. The findings demonstrate a persistently elevated oxidative burden across the cohort, with minimal modulation by hydroxyurea

therapy, disease severity, or socioeconomic class.

The significantly lower WBC count observed among HU users is consistent with the known myelosuppressive and anti-inflammatory effects of hydroxyurea and has been widely reported in previous studies.^{21,22} This reduction is clinically relevant, as leukocytosis is a known contributor to vaso-occlusion and disease

Figure 1: Oxidative Stress Burden in Paediatric Sick Cell Anaemia: Effects of Hydroxyurea Therapy, Disease Severity, and Socioeconomic Factors



severity in SCA.^{23,24} However, despite this favourable haematological effect, HU use was not associated with statistically significant reductions in oxidative stress markers or improvements in antioxidant capacity in this cohort. Conceding that HU modulates oxidative stress in SCA children, it is possible that this antioxidant effects lag its myelosuppressive benefits in these children.

Although children with SCA on HU therapy demonstrated numerically lower MDA levels, the absence of statistical significance suggests that hydroxyurea may only partially attenuate oxidative injury or that its antioxidant effects are insufficient to overcome the chronic oxidative stress intrinsic to sickle cell disease. This aligns with reports indicating that while HU reduces haemolysis and inflammation, oxidative stress may persist due to ongoing red cell sickling, recurrent ischemia-reperfusion injury, and endothelial dysfunction.²⁵

This finding contrasted with works previously reported by Torres et al, Nader et al and Pedrosa et al.¹²⁻¹⁴ where he found a protective effect of HU on oxidative stress. This is probably because the works were done outside of a low resource environment and the cohorts used were adults, not children. Moreover, their works had modest sample sizes reflecting the prevalence of SCA in their environments.

Disease severity was not associated with significant differences in oxidative or antioxidant markers. This finding suggests that oxidative stress is a fundamental feature of SCA, present even in clinically milder phenotypes. Similar observations have been reported by Renoux et al²⁶ who documented that the rate of

vaso-occlusive crisis events in sickle cell anemia was not associated with the level of oxidative stress. Reid et al. and Fasola et al., who also documented elevated oxidative stress markers across SCA patients regardless of clinical severity. However, the small number of participants with severe disease in this study limits definitive conclusions and reduces statistical power to detect subtle differences.

The absence of socioeconomic gradients in oxidative stress markers contrasts with theoretical expectations that lower socioeconomic status might exacerbate oxidative stress through poor nutrition, recurrent infections, or delayed access to care. The relative homogeneity observed may reflect shared environmental exposures, similar dietary patterns, or standardized clinical management within the study population. It is also possible that the overwhelming biological impact of SCA overshadows socioeconomic influences on oxidative balance.

Overall, these findings reinforce the concept that oxidative stress in sickle cell anaemia is multifactorial and deeply entrenched, with limited modulation by hydroxyurea therapy alone. Adjunctive strategies such as antioxidant supplementation, nutritional optimization, and early initiation of disease-modifying therapy may be necessary to achieve meaningful redox balance.

Strengths and Limitations

Strengths

- Comprehensive assessment of both enzymatic and non-enzymatic antioxidants alongside oxidative

stress markers.

- Inclusion of hydroxyurea exposure, disease severity, and socioeconomic status in a single analytical framework.
- Use of a validated disease severity scoring system (Kuti and Adegoke scale).

Limitations

- Cross-sectional design limits causal inference.
- Small number of participants with severe disease reduced statistical power.
- Lack of data on adherence to hydroxyurea therapy.
- Dietary intake and micronutrient supplementation were not assessed.
- Single-time-point biochemical measurements may not reflect long-term oxidative status.

Compliance with Ethical Standards

Funding: None

Conflict of Interest: None

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