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Evaluation of Serum Zinc Level among Yemeni Patients with Sickle Cell Anemia

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Abstract

Background: Sickle cell anemia (SCA) is a genetic disorder characterized by chronic hemolysis, vaso-occlusive episodes, and oxidative stress. Zinc, an essential antioxidant trace element, is vital in countering oxidative damage and maintaining cellular health. This study aimed to assess serum zinc levels and their relationship with hematological parameters in Yemeni patients with SCA.
Materials and Methods: This comparative cross-sectional study was conducted at the Yemen Society for Thalassemia and Genetic Blood Disorders in Sana'a. The study included 104 participants: 52 patients with SCA (HbSS) in steady state and 52 age- and sex-matched healthy controls (HbAA). Serum zinc levels were measured using spectrophotometry and hematological parameters were analyzed using automated hematology analyzers. Statistical analysis was performed using SPSS version 26, with statistical significance set at $P < 0.05$.
Results: SCA patients had significantly lower serum zinc levels (73.8 ± 36.6 µg/dL) compared to controls (96.7 ± 38.7 µg/dL) ($P = 0.003$). Hemoglobin, red blood cell count, and packed cell volume were significantly lower in the SCA group ($P < 0.001$), whereas white blood cell and platelet counts were significantly higher ($P < 0.001$). Weak correlations were found between zinc levels and hemoglobin ($r = -0.122$), platelet count ($r = 0.075$), and WBC count ($r = 0.098$), but none were statistically significant.
Conclusion: This study revealed significant zinc deficiency among Yemeni patients with sickle cell anemia (SCA). Although we observed differences in hematological parameters between patients with SCA and controls, zinc levels showed no significant correlation with these parameters. Further clinical research is needed to determine whether zinc supplementation could benefit SCA patients in Yemen.

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1. INTRODUCTION

Sickle cell anemia (SCA) is a hereditary blood disorder caused by a mutation in the gene encoding the β-globin subunit of hemoglobin. This mutation results in the replacement of glutamic acid with valine at position 6 of the β-globin chain [1]. This alteration in the primary protein structure transforms Hemoglobin A (HbA) into Hemoglobin S (HbS). Under low-oxygen conditions, this change causes red blood cells to assume a sickle shape, leading to vaso-occlusion, which is the blockage of blood vessels. Consequently, this obstruction prevents adequate delivery of oxygen to various tissues and organs [2]. Hemoglobin changes into an insoluble, rigid form when oxygen is not present, which alters the structure and function of red blood cells and gives them a sickle shape [3]. Two main pathophysiological mechanisms-vaso-occlusion leading to ischemia-reperfusion damage

and hemolytic anemia-interplay to produce the clinical manifestations seen in SCA [4]. Hypoxia, ischemia, tissue damage, and inflammation are the end results of vaso-occlusion, a complicated phenomenon that includes the blockage of small blood vessels by sickled red blood cells (RBCs) and attached blood cells, development of intimal hyperplasia in large vessels, thrombosis, and bone marrow fat embolization [5]. Sickle cell disease is one of the most common autosomal recessive diseases in the world [6]. With an estimated prevalence of 329 cases per 1,000,000 people in the United States, 217 cases per 1,000,000 people in the United Kingdom, over 20,000 cases per 1,000,000 people in Nigeria, over 45,100 cases per 1,000,000 among adults in Saudi Arabia, and 2400 cases per 1,000,000 among Saudi children and adolescents, the prevalence of sickle cell disease varies by region [7]. The prevalence Sickle cell gene in Yemen was estimated to be 2.2%, with a gene frequency of over 4.0% among residents of the Taiz and Hajjah governorates [8]. Zinc is an essential mineral that plays a role in many physiological and cellular processes such as cell division, protein and DNA synthesis, and cellular metabolism [9]. Zinc has significant systemic effects, in addition to its activities at the cellular level. These effects include immune function support, wound healing, growth and development, and maintenance of healthy taste and smell perception [10]. It is interesting to note that zinc may protect against premature aging [11]. Furthermore, zinc has antibacterial and antioxidant properties that may help protect the body against microbial and oxidative stress [12]. Furthermore, zinc acts as an anti-sickling agent by successfully blocking the binding of calcium to the membrane of red blood cells, whereas the interaction of calcium with the membrane of red blood cells may contribute to the formation of irreversible sickle cells [9]. One important pathogenic characteristic of SCA is aberrant sickling and morphing of red blood cells, which is prevented by the antagonistic action of zinc [13]. In patients with SCA, disturbances in zinc homeostasis can affect antioxidant defenses and worsen their condition. This study aimed to determine zinc levels in patients with SCA compared to healthy controls, potentially clarifying how zinc contributes to SCA pathophysiology in Yemen.

2. METHODS

2.1. Study Design

This comparative cross-sectional study was conducted by the Yemen Society for Thalassemia and Genetic Blood Bisorders in Sana'a City, Yemen, from July to December 2024.

2.2. Study Population

The study population included patients with SCA (HbSS) and healthy controls with HbAA matched for age and sex.

2.3. Sample Size

The sample size for this study was 104 participants (males and females), calculated using the OpenEpi program (version 2.3.1) with a 95% confidence level and 80% power. The expected mean ± standard deviation of zinc was 70.95±6.33 for patients group and 78.4±6.49 for controls groups, respectively [14]. The sample size was increased to increase the accuracy.

2.4. Data Collection

Individual data were collected using a standardized questionnaire, including anthropometric and medical data, such as age, sex, occupation, and history of the last crisis.

2.5. Sample Collection

Five milliliters of venous blood were collected aseptically via venipuncture. Two milliliters were placed into a labeled ethylenediaminetetraacetic acid (EDTA) tube, while the remaining three milliliters was placed in a labeled dry plain tube. The samples in the plain tube were centrifuged at 3,000 rpm for 5 min to separate the serum. Serum was extracted using a pipette and stored at -20 ℃ until analysis. Blood collected in EDTA was used for complete blood count (CBC) using an auto hematology analyzer (Mindray BC-5000, Germany) and for hemoglobin phenotype determination via Hb electrophoresis using the cellulose acetate technique in alkaline medium (MiniLITE PLUS, Italy). Serum zinc levels were analyzed using a spectrophotometric method (BioSystems BA200, Spain).

2.6. Statistical Analysis

Data were analyzed using the SPSS software version 27 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to compute percentages, proportions, means, and standard deviations. The relationship between the mean values of zinc and blood counts was examined using Pearson's linear regression for bivariate correlations. Statistical significance was set at a probability threshold of $P < 0.05$.

2.7. Ethics Statements

Ethical approval for this study was obtained from the Committee of Postgraduate Studies and Scientific Research of the Faculty of Medicine and Health Sciences. All participants or their parents received a clear explanation of the study aims and procedures, and informed consent was obtained from all the participants.

Table 1. Demographic characteristics of patients with SCA (HbSS) and healthy controls (HbAA)

Parameter	SCA (HbSS) n (%)	HbAA n (%)
Mean age	19.1±9.5	20.9±9.4
Gender		
Male	33 (63.5 %)	31 (59.6 %)
Female	19 (36.5 %)	21 (40.4 %)
Occupation		
Employed	4 (7.7 %)	21 (40.4 %)
Unemployed	48 (92.3 %)	21 (59.6 %)
History of last crisis		
Within 48 hrs.	26 (50 %)	0 (0)
More than one month	26 (50 %)	0 (0)

HbSS : Hemoglobin SS; HbAA : Hemoglobin AA

3. RESULTS

One hundred and four participants were recruited, comprising 52 patients with SCA (HbSS) and 52 HbAA controls. Among the SCA patients, 19 (36.5%) were females and 33 (63.5%) were males, with a mean age of 19.1 ± 9.5 years. In contrast, the control group consisted of 21 (40.4%) females and 31 (59.6%) males, with a mean age of 20.9 ± 9.4 years. Regarding occupation, the majority of SCA patients were unemployed (92.3%), while only 7.7% were employed. In contrast, 40.4% of the control group were employed, and 59.6% were unemployed. Crisis history was only recorded in patients with SCA. 26 patients (50%) had a crisis within the last 48 hours, while the other 26 (50%) reported that their last crisis occurred more than one month prior to the study (Table1)

Patients with SCA had a significantly lower mean zinc level than those in the control group (P = 0.003). Similarly, individuals with SCA exhibited significantly lower hemoglobin (Hb), packed cell volume (PCV), and red blood cell (RBC) counts than those in the control group (P < 0.001). In contrast, patients with SCA showed significantly higher white blood cell (WBC) and platelet (PLT) counts than those in the control group (P < 0.001). Moreover, patients with SCA had a significantly higher mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW-CV and RDW-SD) than those in the control group (P < 0.001). In contrast, absolute neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts were significantly higher in the SCA group than in the control group (P < 0.001). However, there was no significant difference in mean platelet volume (MPV) between the two groups (P = 0.295) (Table 2).

The correlation between serum zinc level and blood count showed a significantly weak positive relationship with hemoglobin (Hb) levels (r = 0.281, P = 0.004). However, there was a weak negative correlation between zinc levels and WBC count (r = -0.090, P = 0.181) and platelet (PLT) count (r = -0.078, P = 0.430), although the difference was not statistically significant (Table 3).

In patients with SCA, the correlation between serum zinc levels and blood counts showed a weak negative relationship with hemoglobin (Hb) levels (r = -0.122, P = 0.389). Additionally, there was a weak positive correlation between zinc levels and WBC count (r = 0.098, P = 0.489) and platelet (PLT) count (r = 0.075, P = 0.596). However, none of these correlations were statistically significant (Table 4).

4. DISCUSSION

An important factor influencing the pathophysiology of SCA is the antioxidant/oxidant state [14, 15, 16, 17], along with the development of vaso-occlusion and reduction in RBC lifespan, which could contribute to the development of dense erythrocytes during the sickling process. Oxidative damage observed in sickled red blood cells is most likely caused by the unstable nature of HbS, which increases the production of oxidation products by promoting the synthesis of free radicals in conjunction with diminished antioxidant defense mechanisms [14, 18, 19]. Findings from this study revealed significantly lower serum zinc levels in patients with SCA (HbSS) than in healthy controls (HbAA). This observation is consistent with previous reports of decreased zinc levels in patients [14, 9, 20, 21]. It has been suggested that the reduced serum zinc levels in SCA patients could be attributed to disrupted metabolism of zinc metalloenzymes, atypical binding of zinc to tissue proteins, and impaired renal tubular reabsorption of zinc resulting from sickling [22, 16, 23]. Patients with SCA have a much higher daily zinc demand owing to hyperzincuria caused by increased hemolysis, which is not satisfied by their typical dietary consumption [22, 24]. Additionally, as bone serves as the primary location for zinc storage, increased bone deterioration in SCA caused by repeated bone ischemia, especially during severe crises, may possibly contribute to increased zinc loss in urine [22, 25]. Therefore, individuals with SCA may lose zinc via a variety of routes. This study also revealed significantly lower RBCs and Hb concentrations and PCV in patients with SCA. This finding is in agreement with the reports of previous studies [22, 26, 27]. The observed reductions in Hb concentration, PCV, and RBCs among patients with SCA are attributable to the chronic hemolysis of red blood cells, which is a hallmark of the disease [22]. This process leads to a shortened survival rate of red blood cells, resulting in lower than normal hematological parameters. Furthermore, the erythropoietic response to anemia is impaired in SCA, leading to a blunted increase in the hemoglobin concentration. This may be due to renal pathology, which can affect erythropoietin production [28]. Interestingly, hemoglobin S has a higher oxygen delivery rate to tissues than hemoglobin A, which may explain why individ-

Table 2. Comparison of Zinc levels and hematological parameters between patients with SCA (HbSS) and healthy controls (HbAA)

Parameters	Mean ±SD		p. value
	HbSS	HbAA	
Zinc (µg/dl)	73.8±36.6	96.7±38.7	0.003
Hemoglobin level (g/dl)	9.5±1.5	14.6±1.4	< 0.001
Red blood cell count ($\times 10^{12}$/L)	3.2±0.8	5.7±0.7	< 0.001
Packed cell volume (%)	29.9±4.7	48.6±4.4	< 0.001
Mean corpuscular volume (FL)	94.7±13.8	85.1±5.9	< 0.001
Mean corpuscular hemoglobin (Pg)	30.1±5.3	25.6±2.2	< 0.001
Mean corpuscular hemoglobin concentration (g/dl)	31.7±2.4	30.1±0.9	< 0.001
RDW-CV (%)	18.7±3.9	14.4±1.2	< 0.001
RDW-SD (%)	57.7±12.4	40.2±2.7	< 0.001
WBC ($\times 10^9$/L)	9.9±5.7	4.9±1.8	< 0.001
Neutrophil count ($\times 10^9$/L)	5.5±4.6	2.6±1.5	< 0.001
Lymphocyte count ($\times 10^9$/L)	3.5±1.9	1.8±0.4	< 0.001
Monocyte count ($\times 10^9$/L)	0.9±0.5	0.4±0.2	< 0.001
Eosinophil count ($\times 10^9$/L)	0.3±0.3	0.2±0.2	0.04
Basophil count ($\times 10^9$/L)	0.02±0.3	0.01±0.01	0.03
Platelet count ($\times 10^9$/L)	371.6±132.7	262.4±50.5	< 0.001
Mean Platelet volume (FL)	9.4±1.1	9.2±0.8	0.295

RDW-CV: Red cell distribution width coefficient of variation
RDW-SD: Red cell distribution width standard deviation.

Table 3. Correlation between zinc and hematological parameters among patients with SCA (HbSS) and healthy controls (HbAA)

Parameter		Hb	WBCs	PLT
Zinc	r	0.281	-0.090	-0.78
	P- Value	0.004	0.181	0.430

Hb, Hemoglobin; RBCs: Red blood cell count
WBCs, white blood cell count; PLT: Platelet count.

Table 4. Correlation between zinc and hematological parameters among patients with SCA (Hemoglobin SS)

Parameter		Hb	WBCs	PLT
Zinc	r	-0.122	0.098	0.075
	P- Value	0.389 0.489	0.596	

Hb, Hemoglobin; RBCs: Red blood cell count
WBCs, white blood cell count; PLT: Platelet count.

uals with SCA can maintain stability at lower hemoglobin concentrations. However, increasing the PCV above 30% can lead to increased blood viscosity, potentially triggering vaso-occlusive crises and other adverse outcomes [22]. The current study revealed a significant elevation in the MCV values in patients with SCA, which is consistent with previous reports [29, 30, 31]. Macrocytosis in SCA represents a significant haematological phenomenon with far-reaching implications. Macrocytosis, characterized by an elevated MCV, is attributed to an increase in reticulocytes, which are young immature red blood cells. This process serves as a crucial adaptive response in the context of SCA, and its underlying mechanisms provide insights into the complex interplay between hemolysis, hematopoiesis, and the unique pathophysiology of sickle cell disease. The present study observed that the mean corpuscular hemoglobin (MCH) level was significantly higher in SCA patients than in HbAA controls. Similar results were reported in a previous study [31]. The present study also found that mean corpuscular hemoglobin concentration (MCHC) was significantly higher in patients with sickle cell than in the HbAA control group. Similar findings were reported in previous studies [32, 33, 34]. The MCHC is a measure of the amount of hemoglobin present per unit volume of packed red cells. Elevated MCHC levels have been observed to be associated with increased red cell sickling, rigidity, and reduced deformability. This phenomenon is likely attributable to the fact that high MCHC levels facilitate the polymerization of sickle hemoglobin, thereby exacerbating the pathophysiology of sickle cell disease [32]. RDW-CV and RDW-SD were also found to be significantly elevated in patients with SCA compared with HbAA controls. This finding is consistent with those of previous studies [32, 35]. Elevated RDW values suggest that sickle cell anemia is associated with marked anisocytosis, which may be attributed to the rapid erythropoiesis that occurs in response to hemolysis, resulting in the presence of cells at different stages of maturation and varying sizes in the peripheral blood [32]. The mean total WBC count in patients with SCA was significantly higher than that in patients with HbAA. This finding aligns with previous studies that also reported elevated total white cell counts in individuals with SCA [22, 36, 37]. The increased WBC count may be attributed to the redistribution of leukocytes between the marginal and circulating pools, influenced by factors such as pain, anxiety, and inflammation, even in the absence of infection [22, 36] . Additionally, leukocytosis in SCA may result from autosplenectomy due to recurrent splenic vessel occlusion [22, 38]. Neutrophil, lymphocyte, and monocyte counts are also significantly elevated in patients with SCA. Similar results were reported in a previous study [39]. Eosinophil and basophil

counts were slightly, but significantly, higher in the SCA group than in the control group. This study also found that the mean platelet count was significantly higher in patients with SCA than that in the control group. Similar findings have been reported previously [22, 32, 27] . In adult individuals with SCA, the increased platelet count may be attributed to the loss of the splenic platelet pool due to autosplenectomies. Additionally, thrombocytosis in SCA may result from the negative feedback effect of erythropoietin production in response to anemia. Given that thrombopoietin shares structural similarities with erythropoietin at the N-terminal end, thrombocytosis has been associated with chronic anemia [40]. The limitations of this study include the inability to quantify food intake due to the individuals' inability to precisely recall the number of meals consumed and the lack of urine zinc level, which is a stronger indicator of zinc loss.

5. CONCLUSION

This study demonstrated that Yemeni patients with SCA had significantly lower serum zinc levels than healthy individuals. Additionally, patients with SCA exhibited significant hematological abnormalities, including lower hemoglobin levels, RBC counts, and packed cell volume, along with elevated WBC and platelet counts. The analysis revealed minimal correlations between Zinc levels and hematological parameters, with no statistical significance observed in these relationships. Our findings indicate that additional comprehensive research would be beneficial in determining the efficacy of zinc supplementation on hematological markers and patient outcomes in individuals with SCA.

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