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Evaluation of Liver Function Tests, Parathyroid Hormone, Vitamin D, Calcium, and Phosphorus, in Sudanese Children with Sickle Cell Disease

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Abstract:-

Background: Sickle cell disease (SCD) is a serious public health problem. Chronic liver disease and renal failure are among the secondary end-organ issues that sickle cell disease patients may encounter. This study aims to evaluate the variations of biochemical parameters among Sudanese children with SCD.

Material and Method: This case-control research enrolled 60 children diagnosed with sickle cell disease**,** and 20 healthy individuals were taken as control. The study was conducted at Jaafar Ibn Aouf Pediatric Hospital-Khartoum, Sudan, from November to December 2023. Liver function tests, Parathyroid hormone (PTH), and vitamin D were estimated. Calcium (Ca) and phosphorus (P) levels were assessed.

Results: Compared to the control group, SCD children had significantly higher PTH and P (p-value <0.05). Also, SCD children reported decreased calcium and vitamin D levels compared to the control group, and the p-value for each parameter was insignificant, more significant than 0.05. LFTs between SCD children and control groups showed that SCD children had higher levels of total and direct bilirubin than control, with a significant difference (p-value <0.05) for each group.

Conclusion: Reduced calcium and vitamin D levels are caused by many variables associated with sickle cell disease (SCD) and its management. Elevated phosphorus and parathyroid hormone (PTH) levels have been related to several underlying mechanisms associated with SCD and its consequences.

***Keywords*:** Vitamin D; Parathyroid Hormones; Liver function test; Sickle cell disease; Sudan.

Introduction

Sickle cell disease (SCD) is a predominant hematological disorder and one of the autosomal recessive hemoglobinopathies group [1,2]. The origins of sickle cell disease (SCD) result from the inheritance of two defective beta-globin genes. This leads to hemoglobin polymerizing and crystallization, making erythrocytes stiff and taking on a crescent form in low-oxygen situations prone to hemolysis [3-7]. Medical literature describes SCD as a severe illness that carries a significant risk of hemolytic anemia, respiratory abnormalities, progressive multiple end-organ dysfunctions, and eventually increased mortality cases [4,8-10]. SCD is most widespread, and it was estimated that there are about 100,000 SCD patients in the United States; studies confirmed that SCD can affect one in every 2,070 live births in the United States; large portions of sub-Saharan Africa, the Mediterranean basin, the Middle East, and India are highly endemic to SCD, which may be related to the high amount of protection offered against severe malaria. [11-13]. In Sudan, the Messiria tribe, which originated in western Sudan, has a greater prevalence of SCD in the country [14]. This is according to Y-chromosome haplogroup analysis, which suggests that during the large-scale migrations, it might have been brought explicitly by males of migrant West African tribes, especially Hausa-Fulani and Bagara, that started in the eighteenth century and increased during the nineteenth and early twentieth century [15]. Patients with sickle cell disease may experience various secondary end-organ problems, such as chronic liver disease and renal failure due to microvascular destruction and persistent hemolysis [16]. Hepatopathy related to sickle disease is not rare, but severe sickle cell disease complications [17]. A study by Uche et al. (2022) determined that Hepatic signs were more significant in sickle cell anemia patients [18]. Also, Levesque et al. (2020) detected in their study that patients with sickle cell disease frequently experience liver problems [19]. Vitamin D is a crucial biological element, a significant regulator of calcium homeostasis and bone metabolism [20]. According to previous studies, vitamin D deficiency (VDD) and SDC are significantly correlated. Patients with sickle cell disease have a significant prevalence of vitamin D deficiency; hence, vitamin D supplements may help to prevent and improve deficiency [21,22]. So, patients with SCD frequently suffer from vitamin D deficiency, and those with lower levels of the vitamin are more likely to be anemic [23]. Research has also shown that individuals with sickle cell anemia who undergo frequent transfusions may display a notable deficit of vitamin D [24]. The findings indicated that the group with sickle cell anemia patients tended to hypocalcemia, which was associated with supernormal parathyroid hormone

levels; they also added that the abnormalities in skeletal structure seen in sickle cell patients might be related to the compromised calcium metabolism caused by poor intestinal absorption of calcium [25,26]. The recognition of the parathyroid hormone, liver function, and VDD prevalence in Sudanese patients with SCD may provide fresh knowledge and statistics on the appropriate intake of vitamin D medications in this vulnerable population. Hence, to recognize the association between these variables, this study aims to evaluate the variations of parathyroid hormone, vitamin D, and liver function in Sudanese patients with SCD.

Materials and methods

Study participants

This case-control study enrolled 60 children diagnosed with sickle cell disease; 32 (53.3%) were males and 28 (46.7%) were females; they were further divided into two groups based on the diagnosis duration: those under three years and those over three years. The study was conducted at Jaafar Ibn Aouf Pediatric Hospital, Khartoum, Sudan, from November to December 2023. Jaafar Ibn Aouf Hospital is a pediatric tertiary hospital caring for referred sickle cell disease cases of children; the study participants were divided into two groups: the case group included 60 patients with sickle cell disease, and 20 healthy individuals were taken as control. Patients suffering from hematological malignancy, hemoglobinopathy, and other types of anemia were excluded from the study. Participants (cases and controls) signed an informed permission form and completed a questionnaire to provide their medical history. Five ml of venous blood was collected from each arm of the study group in heparinized containers under septic circumstances. After allowing the blood sample to coagulate; and centrifuging the blood samples at 3000 rpm for five minutes; the plasma samples were collected and preserved frozen at (-20 °C) until the analysis time of liver function tests by (Mindray BS200, 747 S. 13th Street, Boise, USA). Parathyroid hormone (PTH) and vitamin D via enzyme-linked sorbent immunoassay (ELISA) (Biosystems Diagnostics Pvt. Ltd., India). The levels of Calcium (Ca) and phosphorus (P) levels were estimated by using (Mindray High-Tech Industrial Park, Nanshan, Shenzhen, 518057, P. R. China).

Ethical considerations:

Alzaiem Alazhari University ethics board in Khartoum, Sudan, authorized this study; all the participants signed informed consent and completed a structured questionnaire to provide information about their medical history and socio-demographics.

Statistical analysis

The data was analyzed using the Statistical Package of Social Science (SPSS) version 22. The data were reported as mean ± S.D. The results are presented as tables. The sample size was determined to achieve a difference of 5% at $\alpha = 0.05$ and 80% power. was considered A P-value of (<0.05) statistically significant.

Result

The result revealed that SCD children's age means was 6.1±2.6 years. Data were divided into two groups in terms of the diagnosis duration (≤ 3 years (46.7%) and >3 years (53.3%) as shown in **Table. 1. Table 2.** explained a significant increase (p-value <0.05) in the PTH, P, Ca, and vitamin D levels among cases compared with the control group. In contrast, Ca and vitamin D levels measured an insignificant increase among the control group (p-value was >0.05) for each parameter. There was no significant difference between males and females in terms of PTH, Ca, and Vit D levels, and males had lower P levels than females, as shown in **Table 3**, where the p-value for each was (>0.05). When comparing the measured LFT parameters

between the case and control groups, as revealed in **Table 4**, it was found that the cases had higher levels of total and direct bilirubin than the controls, indicating a significant difference for each group (p-value = 0.000). **Table 4** also shows that total protein was lower, and albumin was higher in the case group compared to the control, with a significant difference for each. Although the case group's liver enzyme levels were more significant than the control groups, only ALT demonstrated a significant finding (p-value <0.05). At the same time, ALP and AST displayed insignificant findings (p-value >0.05). Comparing LFTs by gender showed no significant alteration (p-value >0.05) between male and female readings, as indicated in **Table 5**. The Age shows a negative Pearson's correlation with PTH, Ca, ALP, and ALT and a positive correlation with the other parameters; the only one with a significant difference (p-value <0.05) is vitamin D. As displayed in **Table 6**, the duration of diagnosis has negative correlations with PTH, Ca, Vit D, ALP, and ALT, and only Vitamin D has a significant difference (p-value <0.05). In contrast, the other parameters have positive correlations, with no significant difference found for any.

Table 1: Distribution of duration of diagnosis group in case

Duration of diagnosis	Frequency	Percent
≤ 3 years	28	46.7
> 3 years	32	53.3
Total	60	100.0

Table 2: Comparison of PTH and P between case and control

Parameters	**Study population**		**P. value**
	Case	**Control**	
PTH pg./mL	76.2 ± 6.9	23.1 ± 2.6	0.000
P mg/dL.	4.4 ± 1.3	3.9 ± 0.5	0.007
Ca	9.0 ± 0.8	9.6 ± 0.3	0.126
Vitamin D	35.2 ± 19.7	38.7 ± 6.1	0.664

Table 3: Comparison of PTH and P according to gender

Parameters	**Gender**		**P. value**
	Male (n=32)	Female (n=28)	
PTH pg./mL	76.0 ± 7.2	76.4 ± 6.6	0.811
P mg/dL.	4.2 ± 1.2	4.6 ± 1.4	0.234
Calcium	9.2 ± 0.8	8.8 ± 0.8	0.057
Vitamin D	38.8 ± 20.1	31.1 ± 18.6	0.133

Table 4: Comparison of LFT between case and control

Parameters	**Study Population**		**P. value**
	Case (n=60)	**Control** (n=20)	
Total Bilirubin (TB) (mg/dl)	2.7 ± 0.8	0.5 ± 0.2	0.00

Direct Bilirubin (DB) (mg/dl)	1.1 ± 0.4	0.2 ± 0.1	0.00
Total protein (TP) (g/dl)	7.6 ± 0.7	8.5 ± 0.7	0.00
ALB (g/dl)	4.2 ± 0.5	3.6 ± 0.8	0.004
ALP (U/L)	115.7 ± 39.5	99.8 ± 24	0.094
AST (U/L)	20.0 ± 8.6	17.5 ± 6.2	0.233
ALT (U/L)	19.9 ± 6.9	12.7 ± 3.7	0.00

Table 5: Comparison of LFT according to gender.

Parameters	**Gender**		**P. value**
	Male (n=32)	**Female** (n=28)	
TB (mg/dl)	2.6 ± 0.8	2.8 ± 0.7	0.465
DB (mg/dl)	1.1 ± 0.3	1.2 ± 0.4	0.577
TP (g/dl)	7.6 ± 0.6	7.5 ± 0.7	0.497
ALB (g/dl)	4.3 ± 0.6	4.2 ± 0.5	0.691
ALP (U/L)	114.9 ± 37.7	116.5 ± 42.2	0.880
AST (U/L)	21.7 ± 8.3	18.1 ± 8.7	0.100
ALT (U/L)	18.5 ± 6.1	21.5 ± 7.5	0.095

Table 6: correlations of ca, vitamin D, PTH, and LTF with age and duration of diagnosis.

Parameters	**Age**		**Diagnosis duration**	
	R-value	**P-value**	**R-value**	**P-value**
PTH	-0.150	0.253	-0.104	0.429
Ca	-0.011	0.932	-0.046	0.73

Vit D	-0341	0.008	-0.363	0.004
TB (mg/dl)	0.216	0.098	0.216	0.098
DB (mg/dl)	0.132	0.316	0.156	0.235
TP (g/dl)	0.056	0.67	0.117	0.372
ALB (g/dl)	0.170	0.193	0.231	0.076
ALP (U/L)	-0.159	0.226	-0.240	0.065
AST (U/L)	0.235	0.071	0.246	0.056
ALT (U/L)	-0.242	0.063	-0.172	0.190

Discussion

According to the current study, there was a substantial rise in Parathyroid Hormones in SCD compared to the control (76.2±6.9 and 23.1± 2.6 pg./mL), with a p-value <0.05. Based on the measurements of PTH, P, Ca, and vitamin D between the case and control groups, the P level revealed a significant alteration (p-value = 0.007) in the patient's group compared to the control (4.4 ± 1.3 and 3.9 ± 0.5), and this goes with El-Masry (2020) and Abdrabo, A. et al (2021) studies [25,27] which showed that phosphorus level in case group was significantly elevated (6.6 + 1.8 mg/dl) than that of the control group (3.9 + 0.82 mg/dl). The case group's Calcium and vitamin D levels somewhat declined but were not significantly different (p-values = 0.126 and 0.664), respectively; this finding matched with Badr et al. (2020) [28] study, which revealed that Vitamin D deficiency is the most common in patients with sickle cell disease. When comparing measured parameters, according to gender, males had higher levels of PTH, Ca, and vitamin D, and males had lower Phosphorus levels than females. However, there was no significant difference between the two groups. When comparing some of the measured LFT parameters between the case and control groups, the p-value was (<0.05), indicating a significant difference. Both total and direct bilirubin were insignificantly (p-value >0.05) greater in the cases than in the controls. The case group had higher liver enzymes than the control, while only ALT revealed a significant difference (p-value <0.05), and both ALP and AST showed an insignificant difference (p-value >0.05); this is related to the study conducted by Ikegwuonu et al. (2023) [29] study, and disagree with JOHN KENNEDY et al. (2022) [30]

study which revealed a significantly different of albumin (p-value <0.05) in ALP, and AST. Additionally, total protein and albumin were lower among the case group than in controls, with an insignificant difference for each group (p-value >0.05); this goes with studies of Ibrahim et al. (2024) and Nouraie et al. (2020) [31,32] (2024) which revealed hypoalbuminemia in SCD patients. When LFTs were compared by gender, there were no significant variations between male and female readings; thus, no significant difference was found. According to Pearson's correlation analysis, there is a negative relationship between Phosphorus and age and the length of diagnosis. According to Pearson's correlation, the current study also determined that age negatively correlates with PTH, Ca, ALP, and AST and positively correlates with the other parameters. Only vitamin D has a significant difference (p-value 0.008), and duration of diagnosis has negative correlations with PTH, Ca, vitamin D, ALP, and ALT. While the other parameters have positive correlations, and no significant difference was found for any of the parameters.

Conclusion: Lower levels of vitamin D and calcium can be attributed to several factors related to sickle cell disease (SCD) and its treatment, including increased bone turnover and mineral loss, nutritional deficiencies, decreased sun exposure, and medications. At the same time, some children with SCD have elevated levels of phosphorus and parathyroid hormone (PTH), which can be linked to multiple underlying mechanisms related to the disease and its complications.

Competing Interests: The authors declare that they have no competing interests.

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