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The Relation of Vitamin D Deficiency to Vaso Occlusive Crisis in Patients with Sickle Cell Disease

Thesis

Submitted for Partial Fulfilment of Master Degree in Clinical Hematology

By

Mohamed Saiid ElMaadawy
MB.B.CH

Under Supervision of

Prof. Shaza Abdelwahab Ahmed ElKourashy
Professor of Internal Medicine and Clinical Hematology
Faculty of Medicine - Ain Shams University

Dr. Rasha Kamel Fathy
Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine - Ain Shams University

Dr. Mary Gamal Naguib
Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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Mohamed Saiid ElMaadawy

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List of Abbreviations

ACS	**:**	Acute Chest Syndrome
AMPA	**:**	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
CAMP	**:**	Cathelicidin Gene
CDK	**:**	Cyclin/cyclin-Dependent Kinase
CYP	**:**	Cytochrome P450
DRIs	**:**	Dietary Reference Intakes
EMT	**:**	Epithelial-Mesenchymal Transition
FGF 23	**:**	Fibroblast Growth Factor 23
HbA	**:**	Hemoglobin A
HbA2	**:**	Hemoglobin A2
HbF	**:**	Hemoglobin F
HbS	**:**	Hemoglobin S
HbSC	**:**	Haemoglobin C
HbSD	**:**	Haemoglobin D
HbSE	**:**	Haemoglobin E
HbSβ^0	**:**	β-Thalassemia Mutation
HPLC	**:**	High-Performance Liquid Chromatography
NMDA	**:**	N-methyl-d-aspartate
NO	**:**	Nitric Oxide
NSAID	**:**	Non-Steroidal Anti-Inflammatory Drugs
PTH	**:**	Parathyroid Hormone
QOL	**:**	Quality of Life
QST	**:**	Quantitative Sensory Testing
RAS	**:**	Renin-Angiotensin System

RBCs	**:**	Red Blood Cells
SCD	**:**	Sickle Cell Disease
SOC	**:**	Store-operated Ca^{2+} Channel
sVCAM-1	**:**	Soluble Vascular Adhesion Molecule-1
VDR	**:**	Vitamin D-Receptor
VDREs	**:**	Vitamin D-Responsive Elements
VEGF	**:**	Vascular Endothelial Growth Factor
VOC	**:**	Vaso-Occlusive Crisis
25-OHD	**:**	25- hydroxy-vitamin D
7-DHC	**:**	7-dehydrocholesterol

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Abstract

Background: Sickle cell disease (SCD) is a genetic disorder caused by the substitution of the amino acid Valine in place of glutamate at position 6 of the hemoglobin chain, which results in significant hemoglobin instability, solubility, and morphological changes -in the form of misshapen red blood cells that are incapable of normal oxygen exchange. SCD is associated with a number of acute and chronic health problems such as acute infections - attacks of severe pain, "sickle cell crisis" - stroke and there is an increased risk of death.

Objective: To assess the relation between vitamin D insufficiency and the incidence of vasoocclusive crisis among Sickle cell disease patients.

Patients and methods: This study is a cross-sectional study performed from June 2019 to June 2020. The study was conducted at Ain Shams University hospital in the hematology department and the outpatient clinics. A total of 30 SCD patients were enrolled in the study.

Results: In this study a significant correlation was found between vitamin D deficiency, frequency and severity of VOC episodes. A significant correlation was also found between patients' quality of life and vitamin D deficiency. Regression analysis had shown that there is an independent correlation between vitamin D level and VOC severity and frequency. There was a positive correlation between pain severity (according to Numeric rating scale) and annual transfusion frequency; patients who had more severe pain received more blood transfusions per year than those who had mild or moderate pain ($p < 0.001$). There was also a significant correlation between Hb S, Hb F levels, and crisis pain severity; patients who had severe pain had higher Hb S and had lower Hb F levels compared to patients who had mild or moderate pain.

Conclusion: Vitamin D deficiency is an major health problem in patients with sickle cell disease that may exacerbate the disease, severity of crisis episodes, and increases the risk of complications. Monitoring of vitamin D level and treating deficiencies are warranted as primary care point in patients with SCD.

Keywords: Vitamin D Deficiency, Vaso Occlusive Crisis, Sickle Cell Disease

Introduction

Sickle cell disease (SCD) is a genetic disorder that is caused by the improper insertion of the amino acid valine in place of glutamate at position 6 of the hemoglobin chain. This seemingly small error results in significant hemoglobin instability, solubility changes and morphological changes in the form of misshapen red blood cells that are incapable of normal oxygen exchange. SCD presents most frequently among people of black African descent; however, the heterozygous form is a genetic adaptation to increase malaria resistance and it can be found anywhere that malaria is endemic, e.g., Africa, the Middle East, the eastern Mediterranean region and India ***(Hoyland et al., 2011; Rotz et al., 2013).***

The clinical hallmark of SCA is the painful acute ‘‘crisis’’, which despite therapeutic advances, continues to be a treatment challenge. Such crises occur with variable frequency and duration and they commonly require hospitalization. The pathobiology of SCD is characterized by episodic vascular occlusion, with multiple inciting events beyond actual HbS polymerization and mechanical obstruction induced by sickled RBCs. An important mechanism of pain induction

is thought to involve bone marrow vasculature infarction, leading to the release of inflammatory mediators that in turn stimulate afferent nerve fibers and cause pain. Vaso-occlusion also involves adherence of circulating blood elements, such as leukocytes, to endothelial cells, hypercoagulability, endothelial dysfunction, altered nitric oxide (NO) metabolism and ischemia-reperfusion injury ***(Hebbel et al., 2004; Satyen et al., 2006; Aslan et al., 2007).***

Vitamin D is a fat-soluble vitamin naturally present in very few foods, added to others and available as a dietary supplement. Because most humans can receive adequate levels of vitamin D from sun exposure, vitamin D is often considered to be a prohormone as opposed to a true vitamin. Although there is insufficient evidence to prove that vitamin D supplementation will prevent bone fractures in healthy vitamin D sufficient populations, in vitamin D insufficient populations, vitamin D is important in bone mineralization and deficiency can result in bone fractures, musculoskeletal pains and muscle weakness ***(Aslan et al., 2007; Qari et al., 2007).*** Studies have shown marked vitamin D (25(OH) D3) deficiency among SCD patients ***(Hebbel et al., 2004;***

Satyen et al., 2006; Hoyland et al., 2011). Rovner et al. (2008) found that African American children with SCD had higher rates of vitamin D deficiency when compared to non-SCD African-American children living in the same neighborhoods and this same report suggested that poor diet that is related to low socioeconomic status was not associated with observed vitamin D deficiency. Several mechanisms have been suggested as the likely cause of the low serum 25(OH)D3 concentrations among SCD patients, such as low cutaneous synthesis, decreased intestinal absorption, disturbance of adipose tissue metabolism and chronic hemolysis, resulting in bilirubin deposition, among others ***(Goodman et al., 2010; Hassell and Kathryn, 2010; Rotz et al., 2013).*** Patients with circulating levels of 25(OH)D3 less than 14.1 ng/mL reported having more crisis-related hospital visits per year (10) than patients with 25(OH)D3 serum levels >34 ng/mL.