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VITAMIN D DEFICIENCY AND ITS ASSOCIATION WITH INFLAMMATORY MARKERS IN SICKLE CELL DISEASE PATIENTS: A TERTIARY CARE HOSPITAL STUDY.

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Abstract
We investigated vitamin D deficiency in sickle cell disease patients and its association with inflammatory parameters. The study included 64 patients (33 SS and 31 SB) and 21 carriers (AS). Blood was obtained to assess levels of vitamin D, CRP, IL-6, The patients were grouped according to their genotype (SS, SB) and vitamin D status (low or normal). Carriers were also grouped as low or normal vitamin D. Laboratory findings were similar between low and normal Vit D groups in SS, SB and AS genotypes Acute chest syndrome was more frequent in SS-low Vit D (63%) compared to SS-normal Vit D (25%), SB-low Vit D (21%) and SBnormal Vit D (33%) (P = 0.045). Vit D was not a modifier of selected inflammation in sickle cell disease. Acute chest syndrome was comparably more frequent in SS-low vitamin D.

Keywords Sickle cell disease, Genotype (SS, SB and AS) , Vitamin D, IL6, CRP ,Inflammatory parameter, Low Vit D group and Normal vit D group

Introduction

Sickle cell disease (SCD) and its different forms are genetic conditions where a person inherits a faulty version of a protein called hemoglobin, known as HbS. When this abnormal hemoglobin becomes stiff under certain conditions like low oxygen, acidosis, or dehydration, it causes the red blood cells to change shape, leading to blockages in blood vessels and damage to the blood vessel walls along with inflammation in the bloodstream. This inflammation is shown by higher levels of certain markers of inflammation, such as C-reactive protein (CRP) and various cytokines, both in people who are stable and those experiencing a crisis, compared to those without the diseases. Studies have also reported higher levels of specific cytokines in the blood of stable patients, like IL-1, IL-6, and IFN-gamma, and in crisis patients, like TNF-alpha and IL-6.

Cytokines are divided into two main groups—pro-inflammatory ones like IL-2, IL-12, and TNF-alpha are mainly made by T-helper 1 (TH1) cells and help fight infections inside cells. On the other hand, anti-inflammatory cytokines like IL-4, IL-6, and IL-10 are produced by T-helper 2 (TH2) cells and help combat infections outside cells. Research by Taylor and others found higher levels of IL-6 in stable children with SCD compared to normal children and suggested that there might be an imbalance between pro-inflammatory and anti-inflammatory responses in these patients.

Vitamin D deficiency is very common in people with SCD as shown in several studies. Children with SCD are about five times more likely to have Vitamin D deficiency than those without the condition, even after considering factors like the season and age. While Vitamin D is best known for its role in

bone health, it also has receptors on many immune cells and is thought to play a part in managing inflammation.

Vitamin D helps regulate the immune system by activating macrophages and monocytes, which are part of the body's first line of defense, and by increasing the number of regulatory T cells (Treg) and levels of anti-inflammatory cytokines like IL-4 and IL-10 that are involved in the TH2 immune response.

A lack of Vitamin D in people with SCD could be linked to the ongoing inflammation and blood vessel blockages that are common in the disease. Recent studies have looked into how Vitamin D levels relate to inflammation markers and cytokine levels in people with SCD. In this regard, we conducted a study to explore the connection between Vitamin D status and inflammation in SCD.

Material and Methods

Sixty-four patients with sickle cell disease (SCD) who were being followed up regularly were included in the study between of age 2 to 18 years. The genetic types of these patients were either SS or S-beta thalassemia (SB), determined through high-performance liquid chromatography (HPLC) and genetic testing. Vitamin D deficiency was defined as having a serum 25(OH) D3 level below 20 ng/mL [17]. The patients were divided into four groups: SSlow Vit D, SS-normal Vit D, SB-low Vit D, and SB-normal Vit D. Information about the number of blood transfusions, vaso-occlusive and sequestration crises, hospitalizations, history of hydroxyurea, chelation, and penicillin treatments, as well as cases of acute chest syndrome, stroke, and splenectomy were gathered from each patient's medical records. None of the patients had kidney or liver disease, were taking vitamin D or calcium supplements, or had received a blood transfusion in the three months.

Twenty-one carriers, selected from the patients' relatives, were als last o included in the study as controls.

These carriers were also divided into two groups: AS-low Vit D and AS-normal Vit D. The study was approved by an Ethics Committee, and informed consent was obtained from all participants.

Laboratory Analysis

- Vit D Status was assessed with serum levels of 25-OH-vitamin D3.
- CRP levels were determined by Abbott Architect.
- Levels of Cytokines (, IL-6) were determined by ELISA system.
- Statistics Statistical analysis was carried out using IBM SPSS Statistics 22.
- Data are reported as mean ± standard deviation.
- Statistical significance was set at P\0.05.
- Chi square test was used to assess the difference between descriptive characteristics among group

Results

	SS Thalassemia		SB Thalassemia		AS carrier	
Lab Parameters	Low Vit D	Normal vit D	Low vit D	Normal vit D	Low vitD	Normal vitD
Vit D	11.3±4.2	26.6±4.2	13.1±3.5	26.6±4.8	17.0±1.6	25.1±4.0
IL 6	79.8±30.4	108.7±138.1	96.6±54.8	148.9±183.6	78.4±26.3	135.6±153.2
CRP	4.6±3.3	7.1±4.1	4.7±4.2	5.4±3.4		

The study involved 64 people with sickle cell disease, of whom 33 had the SS genotype and 31 had the SB genotype. There were also 21 people who carried the sickle cell trait with the AS genotype.

1.For those with the SS genotype, there was no big difference in any of the lab tests between people with low vitamin D levels and those with normal levels.

2.For the SB genotype group, people with low vitamin D had significantly lower levels of IL-12 compared to those with normal vitamin D (P = 0.045). However, there was no big difference in IL-6 levels between the two groups.
3.For the AS genotype group, there was no big difference in any of the lab tests between people with low vitamin D and those with normal levels.

Discussion

We thought there might be a connection between low vitamin D levels and ongoing inflammation in people with sickle cell disease (SCD) and did this study to check. We found that vitamin D levels didn't affect most of the lab results we looked at in our SCD patients and their carriers, except that people with low vitamin D had slightly lower average IL-12 levels compared to those with normal vitamin D. The highest number of acute chest syndrome cases was seen In SS patients with low vitamin D compared to those with normal levels. A previous study found that 76% of SCD children had vitamin D deficiency [20]. In our study, we saw a similar rate of vitamin D deficiency, which was 60.95%. In people with atherosclerosis, low vitamin D and high triglyceride levels were linked [18]. Earlier research also showed that vitamin D levels were connected to lower triglycerides and higher HDL in the blood [19]. High triglycerides in SCD were linked to ongoing inflammation [15]. When we compared triglyceride levels between our patients and carriers, regardless of their vitamin D levels, patients had much higher levels.

A study showed that in vitamin D-deficient children with SCD, taking vitamin D daily for three months helped reduce inflammation [13]. They suggested that vitamin D supplements could help reduce inflammation in managing SCD. However, in our study, we didn't find a link between vitamin D levels and inflammation in patients grouped by their genetic type. Patients with SS and low vitamin D had more frequent acute chest syndrome in the past year compared to other groups, which might suggest a connection between low vitamin D and acute chest syndrome in SS patients. SS patients generally have a better outcome than AS patients. There was no previous research on vitamin D levels and history of acute chest syndrome, but a recent study suggested a possible link between vaso-occlusive crises and low vitamin D in SCD patients [23]. A cute chest syndrome happens due to blockages in the lungs of people with SCD who are hospitalized and often have a history of previous blockages [24].
We think more SCD patients should be studied to find out if there's a link between acute chest syndrome and vitamin D deficiency. People with AS genotype are usually not seen as needing treatment because their complications are either rare or mild. A study looked into inflammation during exercise in people with sickle cell trait and found that some of these individuals might show signs of inflammation caused by exercise [25].In another study, people who carried the sickle cell gene (AS) had lower CRP level compared to those with sickle cell disease (SS), and their levels were similar to people with the AA genotype [26].
However, more research is needed to determine if having one sickle cell gene (heterozygous states) affects long-term inflammation or vitamin D levels. One weakness of this study was that there weren't enough participants in each group. Future studies with more people and better tools to measure inflammation could help understand if vitamin D is connected to inflammation, especially in the blood vessel lining, in sickle cell disease.

Conclusion

There is no major impact of vitamin D levels on certain bone, lipid, and inflammation markers found in the blood of SCD patients. However, we noticed a much higher occurrence of acute chest syndrome in SS patients with low vitamin D levels. It's possible that other factors could influence the lab results, but this condition linked to vitamin D deficiency suggests that vitamin D might play a role in how the disease progresses.

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