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Research Article

Association Between Serum 25(OH)D Concentration and Clinical and Biological Complications in Pediatric Patients with Sickle Cell Disease

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Abstract

In addition to its role in phosphocalcic and bone metabolism, vitamin D also plays a global role in health. Despite high levels of sunshine, vitamin D deficiency remains a public health problem in sub-Saharan Africa, where sickle cell disease predominates. This study aimed to investigate an association between serum vitamin D (25(OH)D) levels and the occurrence of clinical and biological complications. The study was carried out in children with SS sickle cell disease aged 1 to 17 years (75 patients) matched to 17 AA controls. Plasma 25(OH)D concentration was obtained by immunoassay. The clinical complications studied were caso-occlusive crisis, osteomyelitis, osteonecrosis, acute chest syndrome, and priapism. Biological parameters included blood count, ionized calcium, and phosphorus. Statistical analysis was performed using R Studio 4.1.2 software. The significance threshold was 5%. Our study revealed a high prevalence of vaso-occlusive crisis (97%). Vitamin D deficiency was found in 4% of patients (3 SS patients) and 36% (27 SS patients) had a plasma concentration between 10 and 30 ng/ml. The association study revealed a negative association between vitamin D and the number of vaso-occlusive crises ($r = -0.51$; $p < 0.001$). We noted a positive association between vitamin D and blood calcium ($r = 0.347$; $p < 0.002$), phosphatemia ($r = 0.347$; $p < 0.002$), and hemoglobin ($r = 0.243$; $p < 0.035$). Vitamin D is correlated with certain clinical and biological complications. Vitamin D supplementation in children with sickle cell disease (SS) would therefore be relevant for better management of this disease.

Keywords

Sickle Cell Disease, Vitamin D, CVO, Ionized Calcium, Hemoglobin

1. Introduction

Sickle cell disease is a monogenic disorder resulting from a mutation in the β-globin gene, characterized by variable clinical symptomatology. It is characterized by an abnormal hemoglobin, hemoglobin S, which results from the point mutation of the

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sixth codon of the β-globin gene, GAG, which is replaced by GTG. The sickle cell gene is pleiotropic, causing multiple phenotypic expressions that constitute the various complications of the disease. Its manifestations may be acute, chronic, nociceptive, or neuropathic, and may occur singly or in combination. Pain continues to be the main factor in the phenotypic complications of sickle cell disease [1]. In addition, people with sickle cell disease have nutritional deficiencies, and vitamin D deficiency is one of the most common. The symptoms of vitamin D deficiency are similar to those of sickle cell disease and include chronic pain, bone complications, and chronic systemic inflammation. What's more, knowledge of vitamin D has progressed considerably in recent years, from a vitamin with a purely phosphocalcium and bone tropism to a pleiotropic hormone with a global role in health (anti-infectious, anti-inflammatory, antitumoral, cardiovascular protective) [2]. Several studies carried out worldwide on the prevalence of vitamin D deficiency show low serum concentrations in sickle cell patients [3]. In Senegal, to our knowledge, we have not found any studies on 25(OH)D status in the context of sickle cell disease, nor its association with certain clinical parameters of sickle cell disease, notably vaso-occlusive crisis (VOCs), and biological parameters, notably calcemia. Given these findings, this study was initiated to investigate vitamin D status in a pediatric sickle cell population, and its correlation with certain clinical and biological parameters.

2. Materials and Methods

This was a prospective analytic study that ran from March 2022 to December 2022 and involved a sample of seventy-five (75) SS sickle cell patients and seventeen (17) AA controls. It was carried out at the Centre Hospitalier National d'Enfants Albert Royer de Dakar (Senegal), more specifically at the Ambulatory Care Unit for Sickle Cell Children and Adolescents. Assays of the various biological parameters were performed at the hospital's medical biology laboratory. All children with malnutrition, hydroxyurea supplementation, or vitamin D supplementation before 25(OH)D determination were excluded from the study. Also excluded were any sickle-cell-affected children with a pathology affecting phosphocalcic metabolism, or who had received a transfusion in the three months before sampling. Clinical data were collected from analysis reports and medical records of patients followed at the hospital. Age, sex, and clinical signs were recorded for each patient. These were VOCs, osteonecrosis, osteomyelitis, acute chest syndrome (ACS), and priapism. As for the biological parameters, we determined the CBC, the calcemia, more precisely the ionized fraction, the phosphatemia, and the vitamin D concentration (25(OH)D). The Mindray BC 5380® (Shenzhen, Mindray Bio-Medical Electronics Co., Ltd, China) was used to determine the blood count (CBC). Ionized calcium, the physiologically active fraction, was determined using the EXIAS e|1 Analyzer (EXIAS Medical GmbH, Graz, Austria). The analyzer used for phosphorus levels was the Biosystems BA400 (Biosystems S. A. Costa Brava, Barcelona, Spain). Vitamin D was measured using the MAGLUMI 600 analyzer (Snibe Diagnostic, Shenzhen, China), which uses a chemiluminescence method. Statistical analysis was carried out using R Studio 4.1.2 software, which enabled us to calculate descriptive data such as mean and standard deviation for quantitative variables, and percentages and sex ratios for qualitative variables. The Student's t-test was used to compare means, and the chi-square test to compare qualitative variables. Pearson's correlation coefficient (r) was used to study correlations. The OODS RATIO was calculated for risk estimation. A P value of less than 0.05 was considered significant. The study was approved by the Ethics Committee of the Cheikh Anta Diop University of Dakar (0079/2015/CER/UCAD).

3. Results

3.1. General Characteristics of the Population

The mean age of the patients was 9.09 years (extremes: 1 and 17 years, standard deviation 4.69). The distribution of patients by age group is shown in graph 1. The age groups with the highest numbers were (5-10) years and (10-15) years, with proportions of 34.66% (26 patients) and 29.33% (22 patients) respectively.

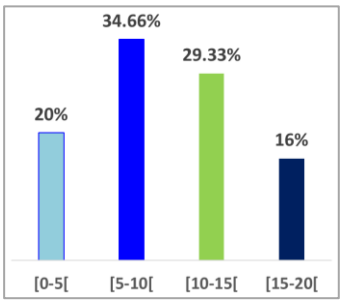
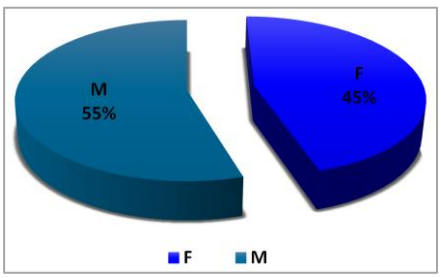


Figure 1. *Age distribution of sickle cell patients.*

The distribution of SS patients by gender revealed a predominance of males, with a total of 41 patients versus 34 females, giving an M/F ratio of 1.20 (Figure 2).



SS patients were age- and sex-matched with AA controls.

Figure 2. *SS patients by gender.*

3.2. Distribution of Patients by Clinical Manifestations

Clinical data showed that 97% of subjects had experienced at least one episode of CVO during the study period. Among the other complications found in our population, osteomyelitis and osteonecrosis were the most frequent, with 15 cases (20%) each (Table 1).

Table 1. *Distribution of patients according to clinical manifestations.*

Clinical manifestations	Effective (N)	Percentage (%)
VOCs	73	97.33
ACS	05	6.66
Osteonecrosis	15	20
Osteomyelitis	15	20
Priapism	01	1.33

VOC =Vaso-occlusive crisis; ACS= acute chest syndrome

3.3. Assessment of Biological Parameters in Our Study Population

The results concerning the means of biological parameters are reported in Table 2. Comparison of the means for biological parameters showed significant differences ($p<0.05$) between SS patients and AA controls, except for vitamin D and erythrocyte constants.

Table 2. *Comparison of the means of the various biological parameters studied between SS patients and AA controls.*

Parameters	Case (N=75)	Controls AA (N=17)	*p*
GB (10^3/mm^3)	17.42 ±6.34	9.15 ±5.27	*0.03**
Hb (g/dl)	7.94 ±1.54	10.97 ±1.49	*0.003**
MCV (fl)	85.06 ±7.88	80.12 ±7.7	*0.0109**
MCH (pg)	28.75 ±3.35	24.24 ±3.15	*0.05*
MCHC (g/dl)	33.77 ±1.96	30.09 ±2.20	*0.120*
Vitamin D (ng/ml)	37.91 ±13.41	35.16 ±13.33	*0.44*
Ionized calcium (mmol/l)	0.86 ±0.12	1.0 ±0.11	*0.0094**
Phosphatemia (mg/l)	51.80 ±16.87	38.33 ±10.19	*0.0022**

WBC: White blood cells; Hb: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration * statistically significant difference

3.4. Assessment of Vitamin D Status in SS Patients

Vitamin status in patients was assessed according to laboratory standards. Deficiency is defined as a vitamin D concentration <10 ng/ml. Vitamin D insufficiency was defined as a concentration of 10-30 ng/ml. Vitamin D deficiency was found in 4% of patients (3 SS patients), and 36% (27 SS patients) had a plasma concentration of between 10 and 30 ng/ml (Figure 3).

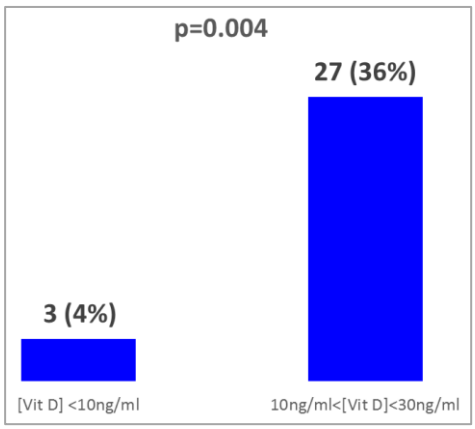


Figure 3. *Distribution of SS patients according to vitamin status.*

3.5. Association Between Vitamin D and Biological Clinical Parameters

Our results on the association study (Table 3) revealed a negative association between vitamin D and the number of vaso-occlusive attacks (r = -0.51; p < 0.001). On the other hand, there was a positive association between vitamin D and serum calcium (r = 0.347; p < 0.002), serum phosphorus (r = 0.347; p < 0.002), and hemoglobin (r = 0.243; p < 0.035). On the other hand, there was no correlation between vitamin D and bone disorders, namely osteonecrosis and osteomyelitis.

Table 3. *Association between vitamin D and clinical and biological parameters.*

		25(OH)D (ng/mL)
VOC	r	0,51
	p-value	< 0,001**
Osteomyelitis	r	1
	p-value	
Osteonecrosis	r	1
	p-value	
Ca^{2+} (mmol/L)	r	0,347**
	p-value	0,002**
Phosphatemia (mg/l)	r	0,347**
	p-value	0,002**
Hb (mg/dl)	r	0,243*
	p-value	0,035*

4. Discussion

The study population consisted of 75 homozygous sickle cell patients aged 1 to 17 years followed regularly at the USAD. We also included 17 AA controls matched in age and sex to SS patients. The mean age of our patients was 9.09 years. Moreover, the age groups with the highest numbers were [5-10[years and [10-15[years, with proportions of 34.66% (26 patients) and 29.33% (22 patients) respectively. These results were similar to those of Sagne et al [4], Thiam et al [5] and Boiro et al [6]. These authors reported respective mean ages of 9.4, 8.12, and 8.26 years. This similarity could be explained by the fact that all these studies were carried out in Senegal, and even better, on the same study population as ours for some of them. It could also be because our patients were recruited from the USAD, which is a unit dedicated solely to the care of sickle-cell-affected children and adolescents. Regarding gender, a male predominance was observed, with 55% of patients male, i.e. a sex ratio of 1.2. These results are similar to those reported by other studies, notably Boiro et al [6] and Y éDiarra et al [7], who found sex ratios of 1.42 and 1.44 respectively. The male predominance we observed could be partly explained by the fact that fetal HbF production is lower in boys, resulting in greater early expressivity of the disease in the latter, according to Labie et al. [8]. It is important to note, however, that sickle cell disease is not a gonosomally transmitted disease [8], i.e. it is not sex-dependent. The male predominance observed in our study could simply be due to chance, without having any direct link with the disease's transmission mechanism. In contrast, Kedy et al [9] in Douala (Cameroon) found a female predominance in their series (sex ratio 1.8).

Regarding clinical parameters, we noted that seventy-three (73) patients, i.e. a prevalence of 97.33%, had at least one episode of CVO during the year 2021-2022, corresponding to the study period. This prevalence observed in our study is comparable to those reported by Diagne et al [10] and Isabelle et al [11], which were 91.83% and 98% respectively. This high prevalence of CVO could be attributed to the fact that vaso-occlusive crisis is one of the most frequent acute complications of sickle cell disease. The other clinical parameters studied were relatively infrequent. There were 20 cases of osteomyelitis and osteonecrosis, representing a prevalence of 20% each. These results appear to be close to those of the study carried out by Thiam et al [5] at the H ôpital de la Paix in Ziguinchor, which revealed a prevalence of 15.07%. These similarities could be explained by the fact that these studies were carried out in the same geographical area. Moreover, the relatively low prevalence may be because osteomyelitis and osteonecrosis are more frequent in adults than in children. Better still, Diagne et al [10] demonstrated in their study comparing the epidemiological and diagnostic aspects of SC and SS forms of sickle cell disease, that the mean age of onset of osteonecrosis is 26 years in SS patients and 30.6 years in SC patients. It should also be noted that children followed at the USAD are often put on antibiotic prophylaxis.

Biological parameters were also studied. These included hematological and biochemical parameters. A mean Hb concentration of 7.9 ± 1.3 g/dL was found in our patients. This concentration was statistically lower than that found in AA controls, who had a Hb concentration of 11.0 ± 1.5 g/dL (p< 0.001). This result is in line with the findings of two other studies carried out in a population of children and adolescents with SS sickle cell disease in Senegal. Indeed, these studies reported mean Hb concentrations of 7.56 ± 1.21 g/dl [5] and 7.80 ± 1.20 g/dL [12]. Our results confirm the anemic character inherent in sickle cell disease, with a significant decrease in Hb concentration in patients compared with controls. In addition, the normocytic normochromic anemia characteristic of sickle cell disease was found, as evidenced by the results of erythrocyte constants. About biochemical parameters, our study revealed a significant drop in ionized calcium in sickle cell patients (0.86 ± 0.12 mmol/L) compared with controls (1.0 ± 0.1mmol/L, a p= 0.0094). These results are corrobo-

rated by those of a study carried out in Nigeria, where the mean ionized calcium concentration in sickle cell patients (2.1mmol/L) was also significantly lower than that in controls (2.3mmol/L, $p < 0.01$) [13]. There are several possible explanations for this drop in blood calcium levels. Studies conducted at the State University of New York by Litosch and Lee. [14] showed that the membranes of sickle cell red blood cells had a higher affinity for calcium than those of normal red blood cells. Another explanation could be a lack of intake or reduced intestinal absorption, probably secondary to the hypovitaminosis observed. Finally, we believe that the drop in blood calcium levels could be due to a calcium deficiency in the bones, which the body tries to compensate for, resulting in a drop in serum calcium concentration. Some studies on bone mineral density (BMD) have already shown in the past a collapse of the latter, such as the study carried out in Iran in 2017 [15] where the apparent bone mineral density (ABMD) of the femoral neck and lumbar spine in sickle cell patients was lower than that of controls; this was also observed in France in 2009 [16]. Although serum phosphorus levels were significantly lower than those of controls, they remained within the usual range. These results seem to be similar to those of Al-hardi's study published in the American Journal of Nephrology [17], where the authors found that the mean serum phosphate value in sickle-cell children was significantly lower than in controls (4.3mg/dL vs. 5.3 mg/dL). However, it should be noted that previous studies have revealed contradictions in the variation of serum phosphorus in sickle-cell patients. Indeed, some studies found hyperphosphatemia, as in Nigeria [13] and the study by Smith et al [18]. Others, such as Chapelon et al [16], reported normophosphatemia. Smith et al [18] indicated that phosphate could be a predictive marker of seizure frequency and that a drop in phosphatemia could bring relief to patients.

Mean vitamin D concentrations were normal in both our patients (37.91 ± 13.41ng/mL) and controls (35.16 ± 13.33ng/mL), based on physiological values ranging from 30 to 70 ng/mL. However, if we assess the vitamin status of our SS patients, we observe both deficiency and insufficiency states. Vitamin deficiency was found in 4% of patients (3 SS patients) and 36% (27 SS patients) had a plasma concentration of between 10 and 30 ng/ml. Our results corroborate the work of researchers who found vitamin D deficiency in sickle cell patients. Indeed, a scientific article published in PLOS ONE in 2015 [19], which was a systematic review study on the prevalence of vitamin D deficiency in sickle cell disease, provided evidence (33 scientific articles) suggesting that low 25(OH) D levels are very common in sickle cell disease patients. And more recently, in 2021, a study in Cameroon [11] also revealed a drop in 25(OH)D concentration in sickle cell patients. This vitamin D deficiency could be explained by unbalanced nutrition (low vitamin D intake) and reduced activity due to repeated attacks. Hypovitaminosis D could also be explained by an excess of hepatic iron caused by recurrent blood transfusions in sickle cell patients. Indeed, some previous studies had shown a negative correlation between low 25(OH)D concentration and ferritinemia in patients with hereditary hemochromatosis and those with thalassemia major and intermedia [20, 21], i.e. the more iron overloaded these patients were, the lower the vitamin D concentration, leading us to speculate that the hypovitaminosis seen in sickle cell patients could be attributable to iron overload caused by transfusions. What, then, are the likely consequences of this deficiency? intensified pain? high susceptibility to infection? recurrent attacks? Our analysis of the correlation between vitamin D and clinical and biological parameters will help us understand the consequences of this deficiency.

Our association studies revealed a strong negative correlation between serum vitamin D concentration and the frequency of vaso-occlusive attacks (Cor=-0.51, p<0.001***). This association corroborates the results of a study carried out in Cameroon in 2021 [11], where researchers found a correlation between serum 25(OH)D levels and CVO. Indeed, these authors obtained a correlation coefficient r = -0.51 and a p-value < 0.001. A study carried out in Nigeria [13] also revealed similar results. This negative correlation observed in our study could be justified by the reduced anti-inflammatory activity of vitamin D. Indeed, previous studies have already demonstrated that inflammation plays an important role in the pathogenesis of vaso-occlusive crises in sickle cell disease [12, 22]. Therefore, considering the anti-inflammatory role of vitamin D, it is plausible that a low 25(OH)D level could intensify inflammation and, by analogy, increase CVO. About the two bone manifestations, the correlation study revealed a lack of correlation between vitamin D concentration and osteomyelitis and osteonecrosis. This result could be explained by the low frequency of these two complications in our study population. However, we believe that a drop in vitamin D could favor osteomyelitis, referring to the anti-infectious action of 25(OH)D, and that it could favor the occurrence of osteonecrosis if we consider the role this vitamin plays in bone metabolism, notably the absorption of calcium and phosphorus by the bones. However, we have not found any scientific article that explicitly mentions a correlation between serum vitamin D concentration and these two manifestations, so it would be interesting to carry out future studies with larger samples to confirm or refute this "potential correlation".

A positive association was observed between serum 25(OH)D levels and hemoglobin concentration, ionized calcium, and phosphorus (Hb; r = 0.243; p=0.035, Ca^{2+}; r = 0.347; p= 0.002, Phosphorus; r= 0.347; p= 0.002). This association between 25(OH)D concentration and low blood calcium levels was expected, as vitamin D plays an important role in the intestinal absorption and utilization of calcium in the body. It is universally recognized as both hypercalcemic and hyperphosphoremic [23, 24]. The positive correlation observed between Hb concentration in sickle cell patients and vitamin D is in line with the findings of a recent study by Grégoire et al [25]. Indeed, these authors demonstrated that sickle-cell children with sufficient vitamin D concentration had higher Hb concentra-

tions compared to children with vitamin D deficiency. Other authors have also reported a positive correlation between these two parameters [26, 27]. We believe that this positive correlation may be due to the role played by vitamin D in regulating cell proliferation and differentiation, since according to some authors, vitamin D promotes the differentiation of several cells, notably blood cell precursors, but also osteoblasts, osteoclasts, chondrocytes, enterocytes and monocytes/macrophages [28, 29]. This could lead to a drop in Hb concentration in the event of vitamin D deficiency.

5. Conclusion

These results highlight associations between vitamin D deficiency and the occurrence of clinical complications such as CVO and biological complications such as calcemia. These associations underline the importance of considering vitamin D deficiency, which could be, alongside other factors such as stress and environmental changes, the underpinning of certain complications in sickle-cell patients. Consequently, it would be pertinent for children with sickle cell disease to be supplemented with vitamin D to prevent possible complications. Further studies are needed to better understand the mechanisms underlying these metabolic disturbances. It would also be interesting to initiate studies to investigate bone density in these vitamin D-deficient children.

Abbreviations

VOC	Vaso-Occlusive Crisis
ACS	Acute Chest Syndrome
BMD	Bone Mineral Density
ABMD	Apparent Bone Mineral Density

Author Contributions

Fatou Gueye Tall: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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