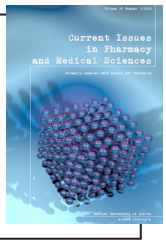
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Impact of Vitamin D in the improvement of respiratory function in sickle cell disease adult patients

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ABSTRACT

The study aimed to discover the role of vitamin D in improving the respiratory function in sickle cell disease patients. In this prospective study, 188 adults were enrolled, drawn from the out-patients unit of Thalassemia Center. The collected data were categorized into three groups: group 1 included the data of 100 healthy individuals of age range of 18-50 years as control; group 2 included the data of 88 (40 males and 48 females) sickle cell disease patients in steady state before supplementation of vitamin D; group 3 represented the data of the same 88 sickle cell disease patients as measured and recorded after 6 weeks of vitamin D supplementation. Laboratory measurements including pulmonary function tests and hematological parameters, while vitamin D levels were estimated for all groups to compare the data before and after supplementation of vitamin We found significant differences in the pulmonary function tests when comparing groups. Mean value of FEV1 revealed significant differences between group 1 and 2 ($p > 0.05$), while vitamin D supplement created a significant difference between group 2 and 3 ($p > 0.05$). The improvement in FEV1 did not reach to that of healthy (group 1), as referred by the significant variation between group 1 and group 3 ($p > 0.05$). The same findings were indicative within most pulmonary function tests, and the percentages of combined cases (restrictive and obstructive) were also deceased in group 3. Conclusion: supplement of vitamin D in SCD patients could result in relative improvement in lung function.

INTRODUCTION

Sickle cell disease (SCD) is a monogenic autosomal resistant disease that comes about due to homozygosity for a mutation in the beta globin chain at position 6 of hemoglobin A (HbA) resulting in sickle hemoglobin (HbS) [1]. Under deoxygenated conditions and polymerization, HbS become less soluble than normal hemoglobin (HbA), and the erythrocytes become rigid and fragile, while display abnormal sickling instead of being biconcave discs. The reduced erythrocyte deformability leads to hemolysis and vaso-occlusive phenomena, thereby hampering their movements through the circulation. This effect results in a much shorter life span than normal [2]. Chronic lifelong hematological disorder, vaso-occlusive phenomenon and intravascular inflammations impact the entire body with multisystem manifestation and organ damage throughout the patient's life. One of the major organs affected is the lungs [3]. In SCD, pulmonary complications manifest as acute chest syndrome (ACS) and as chronic complications, including pulmonary hypertension, hypoxia and pulmonary fibrosis, that ends with respiratory failure. Pulmonary impairment and complications can be detected and confirmed by pulmonary function tests (PFTs) which visualize important parameters in assessing and tracking patients with respiratory pathology and complications [4]. They are also effective in detecting the abnormalities that may develop in respiratory function due to disease or pathological conditions other than respiratory diseases [5-7].

Sickle cell disease has been identified as a pro-inflammatory status characterized by increased body catabolism and undersupply of nutrients intake. Accordingly, sickle cell patients usually suffer from numerous micro and macro nutritional deficiencies, including deficiency of vitamin D [8]. Lack of sunlight exposure, inactivity and glucocorticoids intake all contribute to a decline in vitamin D status in sickle cell patients [9]. Vitamin D (25-hydroxyvitamin D) i.e. 25 (OH) D is a seco-steroid hormone, fat soluble, with notable anti-inflammatory effects that may play a significant role in various diseases involving the respiratory system, as reported by prior study [10]. Vitamin D supplementation in

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sickle cell individuals might lessen the respiratory deteriorations that lead to early death. It has been confirmed that its supplementation is simple, safe and with rare toxicity [11]. All these factors beside the general multiple positive health effects of Vitamin D supplementation encouraged us to conduct this study, as a goal to reveal if its administration may help in improvement of sickle cell respiratory function, as expressed by lung function tests, and reduce the risk of respiratory complications.

MATERIAL AND METHOD

This study is a prospective controlled trial, carried out at Thalassemia Center of Clinical Genetics disorders in Basrah City from November 2021 to end of April 2022. The study protocol and informed consent were duly signed and confirmed by the local ethical committee.

Participants

A total of 200 adult individuals were included in this study and were categorized into three groups: (Group 1) consisted of 100 healthy individuals (47 males and 53 females) at age range 18-50 years, whereas 100 sickle cell disease patients in steady state, who were previously diagnosed as such patients based on electrophoresis and attended the out-patient unit at Thalassemia Center of Clinical Genetics disorders made up group 2. Twelve patients were excluded because they were missing during the follow-up period of the study or were without complete data. The remaining 88 SCD patients (40 males and 48 females) (Group 2) did not receive vitamin D supplementation prior to the study, so they represent the patient group before supplementation of vitamin D. Group 3 consisted of the same 88 SCD patients after supplementation of vitamin D. They agreed to participate in this study and received vitamin D supplementation according to the conditions of the study with commitment to take a specific dose for a specific period so as to enable the obtaining of complete data. Patients categorized in this group received vitamin D supplementation at 50.000 IU./Ml per week for 16 weeks. The work was done in accordance with the World Medical Association's (WMA) Helsinki statement, with the participants' health as the top priority.

Individual characteristics such as age, height, weight, body mass index (BMI), co-morbidities, anamnesis and lifestyle (drug use and smoking status) were collected and recorded using a questionnaire. The BMI was calculated by dividing patient weight (Kg) by their height (m^2). Many exclusion criteria were taken into consideration such as respiratory diseases, cardiovascular diseases, endocrine diseases (thyroid diseases and diabetes mellitus), neuromuscular function disorders, physical abnormalities, as well as smoking.

Laboratory measurements

Laboratory measurements for groups 1 and 2 were performed and documented at the beginning of this study in November 2021, whereas the measurements for group 3 were performed and recorded after 16 weeks of continuous vitamin D administration to compare the data before and after supplementation of vitamin D.

Each participant in this study had a venous blood sample (5 mL) obtained, and 2 ml of blood was collected in an anticoagulated test tube using ethylenediaminetetraacetic acid (EDTA). The remaining blood was collected in a serum separating tube for measurement of vitamin D.

Serum 25-Hydroxyvitamin D

Serum levels of 25-hydroxyvitamin D [25(OH)D3] were measured for the individuals by applying the electrochemiluminescence technique [12] using a Cobas E411 analyzer (India). Deficiency of vitamin D was determined when serum 25(OH)D3 was less than 50 nmol/L (20 ng/ml) [13]. Serum levels less than 75 nmol/L were determined as vitamin D insufficiency(14). Serum levels less than 75 nmol/L were determined as vitamin D insufficiency [14].

Complete blood count

Red blood cell count (RBC); haemoglobin concentration (Hb) (g/dL); mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH); mean corpuscular haemoglobin concentration (MCHC); total count and differential count (neutrophils, monocytes and lymphocytes) of white blood cells (WBC), were all measured via flow-cytometry using a SYSMEX XT-2000i (Japan). Hemoglobin Electrophoresis tests were employed to detect Hb variants [15].

Pulmonary Function Tests Measurements

Spirometry was conducted and interpreted for the participants in compliance with the protocol of the American Thoracic Society (ATS) [16], utilizing a Medical Spirometer (MIR Spiro lab III Diagnostic Spirometer, England). Spirometry was run in a standing position, and the participant was requested to take a complete breath in, followed by as quick and forceful expiration into the mouthpiece of the MIR Spirolab. The procedure depends on individual cooperation, therefore it was repeated three times in order to record the best reading and the correct diagnosis as reported by the instrument, following the standard guidelines [17]. The parameters measured in this study included: forced vital capacity (FVC) in litres; forced expiratory volume in 1 second (FEV1); FEV1/FVC ratio; maximal voluntary ventilation (MVV); peak expiratory flow (PEF) and estimated lung age (ELA). A forceful breathe out of ≥3sec was accepted for interpretation [18]. Absolute values of pulmonary parameters were analyzed to show the changes in the pulmonary parameters among the study groups. The study work was reported in line with the CONSORT criteria. Based on the criteria of ATS [19], spirometry results may illustrate normal, obstructive, restrictive or combined cases. According to the American Thoracic Society (ATS) criteria, normal lung function is defined as FVC and FEV1 being both normal. It is possible that the tested individual's health will decline, resulting in pulmonary concerns. Obstructive lung disease is identified when FEV1 is less than normal, FVC is normal and FEV1/FVC is 70%, a restrictive disease is diagnosed when FVC is 80%, and a combined disorder (restrictive and obstructive disease) is diagnosed when both FVC and the percentage of FEV1/FVC are decreased [20].

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) program version 24.0 was used to analyze the data. Continuous data were represented by means and standard deviations (SD), whereas categorical variables were represented by percentages. Mann-whitney U and Wilcoxon W tests were employed to make the comparison between the means of continuous variables, whereas the nonparametric test (2 independent samples) was applied to analyze categorical variables. P value of less than 0.05 was considered to be a significance variation.

RESULTS

Statistical analysis of characteristics showed non-significant differences in the mean age between group 1 and 2 ($p<0.05$). The gender distribution was close, with 47 percent of men in group 1 and 45.45 percent in groups 2 and 3, with a higher proportion of females in all groups. In contrast, there were significant differences in the means of weight between group 1(healthy group) 72.8±17.60 and group 2 (SCD patients before vitamin D supplementation) (58.63±11.60) and group 3 (SCD patients after vitamin D supplementation) (59.07±11.59), $p>0.05$, but no significant change in the weight of the body between group 2 and 3 ($p<0.05$). The same result was found regarding BMI (Table 1). Vitamin D level was significantly different when comparing between group 1 and 2 (30.08±12.49 *vs*. 18.038±7.50) and between group 2 and 3 (18.03±7.50 *vs*. 30.35±7.02) ($p>0.05$), while it was not significantly different between group 1 and 3 ($p<0.05$), as seen in Table 1.

Table 2 shows that there were significant differences in the pulmonary function tests when comparing between each two groups. Mean value of FEV1 revealed significant differences between group 1 and 2 (3.44±0.80 *vs*. 2.41±0.90) ($p>0.05$). Interestingly, we found that vitamin D supplement created a significant difference between group 2 and 3 (2.41±0.90 *vs*. 2.86±0.72) ($p>0.05$). However the significant improvement in FEV1 did not reach to that of group 1, as indicated by the still existing significant difference between group 1 and group 3 (3.44±0.80 *vs.* 2.86±0.72) ($p>0.05$). We found the same findings related to FVC. There was significant difference between group 1 and 2 (3.83±0.74 *vs*. 2.28±0.76) ($p>0.05$), and significant improvement in group 3 compared to group 2 (3.22±0.73 *vs*. 2.28±0.76) ($p>0.05$). However this improvement did not reach to the level of that of group 1, as referred by the significant difference between group 1 and 3 (3.83±0.74 *vs*. 3.22±0.73) ($p>0.05$) (Table 2). The same profile was reported for PEF and MVV, revealing a significant difference when comparing between each group, as seen in Table 2.

Despite the clear decline in ELA after supplement of vitamin D as referred by the significant differences between group 2 and 3 (55.02±24.22 *vs*. 42.32±17.78), there was still an existing significant elevation in ELA when group 3 (42.32±17.78) is compared to group 1 (35.61±17.10) ($p>0.05$). In contrast, it must be underlined that we noted a significant increase in the ratio of FEV1/FVC. We found no significant difference in this parameter between group 1 and group 3 (98.00±71.07 *vs*. 91.95±10.11) ($p<0.05$), however, there was a significant change between group 2 and 3 (86.01±13.83 *vs*. 91.95± 10.11) ($p>0.05$).

Hematological profile analysis showed significant differences in WBC between group 1 and 2 (7.06±1.58 *vs*. 10.45±4.76) and between group 1 and 3 (7.06±1.58 *vs*. 9.07±3.35) ($p<0.05$), but there was no significant difference between group 2 and 3 ($p<0.05$). The same findings were reported regarding lymphocytes and granulocytes. There were significant differences between group 1 and 2 and 3 ($p>0.05$), while no significant differences were found between group 2 and 3 in these two parameters (Table 3). In contrast, monocytes revealed a different profile from these two parameters, revealing a significant variation when comparing between group 1 and 2 and 3, as well as a significant variation between group 2 and group 3 (0.82±0.55 *vs*. 0.67±0.22) ($p>0.05$).

Regarding RBC, there were significant differences between group 1 and 2 (4.93±0.60 *vs*. 3.34±0.96) ($p>0.05$) and between group 1 and 3 (4.93±0.60 *vs*. 3.55±1.70) ($p>0.05$). No significant difference was found between group 2 and 3 ($p<0.05$). We noted the same findings related to Hb, Lymphocytes and MCV, as seen in Table 3. Interestingly, MCH and MCHC showed an improvement in their levels as represented by significant differences between group 2 and 3 (28.64±4.58 *vs*. 30.42±3.31 and 31.49±3.59 *vs*. 33.43±1.01, respectively) ($p>0.05$).

This study also revealed a variation in the percentage of respiratory cases. Normal spirometry was the highest among other spirometry cases in group 1 (86%), while the percentage of restrictive (mild restrictive cases) was only 8%. In contrast, SCD before supplementation of vitamin D, had higher respective percentages for both mild and moderate (26.13% and 23.86%). The mild restrictive percentage was the highest compared to other cases in group 2. When comparing the spirometry diagnosis percentage between group 2 and 3, we found that normal cases was increased in group 3 (21.59% *vs*. 52.27%), whereas the moderate restrictive percentage was decreased (23.86% *vs.* 17.04%). The percentage of combined cases (restrictive and obstructive) was also deceased in group 3 (18.18% *vs.* 5.68%), as revealed in Table 4.

Table 1. Participants demographics

Parameter	Group 1 Mean ±SD N=100	Group 2 Mean ±SD N=88	Group 3 Mean ±SD N=88	*P value		
				1 *vs* 2	1 *vs* 3	2 *vs* 3
Age (years)	33.51 ±11.04	30.77 ±10.29		NS		
Gender (male:female) Male % Female %	47:53 47% 53%	40:48 45.45% 54.56%				
Weight (Kg)	72.8 ±17.60	58.63 ±11.60	59.07 ±11.59	0.000	0.000	NS
Height (cm)	167.91 ±13.2	162.18 ±10.06		0.001		
BMI (Kg/cm^2)	27.58 ±25.15	21.94 ±3.41	22.19 ±3.31	0.000	0.000	NS
Vitamin D	30.08 ±12.49	18.03 ±7.58	30.35 ±7.02	0.000	NS	0.000

*P is considered significant when the value is >0.05; N: number

Table 2. Comparison of pulmonary function tests among the study groups

Parameter	Group 1 Mean ±SD	Group 2 Mean ±SD	Group 3 Mean ±SD	*P value		
				1 *vs* 2	1*vs* 3	2 *vs* 3
FEV1(L)	3.44 ±0.80	2.41 ±0.90	2.86 ±0.72	0.000	0.000	0.001
FVC (L)	3.83 ±0.74	2.28 ±0.76	3.22 ±0.73	0.000	0.000	0.025
FEV% (L)	98.00 ±71.07	86.01 ±13.83	91.95 ±10.11	NS	NS	0.009
PEF (L/S)	6.51 ±2.15	2.93 ±1.36	4.22 ±1.72	0.000	0.000	0.000
ELA (years)	35.61 ±17.10	55.02 ±24.22	42.32 ±17.78	0.000	0.000	0.000
MVV (L/S)	111.88 ±20.55	73.97 ±26.53	88.71 ±22.25	0.000	0.000	0.000

*P is considered significant when the value is <0.05

Table 3. Hematological parameters comparison among the groups

Parameter	Group 1 Mean ± SD	Group 2 Mean ± SD	Group 3 Mean ± SD	*P value		
				1 *vs* 2	1*vs* 3	2 *vs* 3
WBC (10^9/L)	7.06 ±1.58	10.45 ±4.76	9.07 ±3.35	0.000	0.000	NS
Lymphocytes (10^9/L)	2.57 ± 0.78	3.57 ±2.34	3.55 ±1.70	0.002	0.001	NS
Monocytes (10^9/L)	0.58 ±0.24	0.82 ±0.55	0.67 ±0.22	0.031	0.048	0.032
Granulocytes (10^9/L)	3.86 ±1.39	5.71 ±3.10	4.85 ±2.22	0.036	0.047	NS
RBC (10^12/L)	4.93 ±0.60	3.34 ±0.96	3.55 ±1.70	0.000	0.000	NS
Hb (g/dl)	13.47 ±1.54	9.24 ±2.33	9.82 ±1.45	0.000	0.000	NS
MCV (fl)	88.40 ±6.63	91.90 ±14.22	90.68 ±8.94	0.023	0.027	NS
MCH (pg)	30.88 ±2.96	28.64 ± 4.58	30.42 ±3.31	NS	NS	0.032
MCHC (g/L)	33.94 ±1.40	31.49 ±3.59	33.43 ±1.01	0.000	NS	0.002

*P is significant at value >0.05

Table 4. Percentage of spirometry diagnosis in the groups

Parameter	Group 1 Mean ±SD N=100	Group 2 Mean ±SD N=88	Group 3 Mean ±SD N=88
Obstructive: N (%) Mild Moderate – severe	 5(5%) 0	 9 (8.8%) 0	
Restrictive: N (%) Mild Moderate-severe	 9 (8%) 0	 23 (26.13%) 21 (23.86%)	 22 (25%) 15 (17.04%)
Combined: N (%)	0	16 (18.18%)	5 (5.68%)
Normal respiratory N(%)	86 (86%)	19 (21.59%)	46 (52.27%)

DISCUSSION

The present data were obtained from SCD patients in their steady state before vitamin D supplementation (group 2) and SCD patients after supplementation of vitamin D (group 3) compared to normal healthy people (group 1). One of the main findings was the significant change in vitamin D level between group 1 and group 2, and between group 2 and group 3, Vitamin D deficiency is seen frequently among SCD patients, but its supplement to group 3 turned up its level to be close to that of group 1 (Table 1).

In the present study, beside the increase in the level of vitamin D, there was a significant improvement in pulmonary function test (PFT) parameters measured by spirometry between group 2 and group 3. This improvement was represented by the significant raise in FEV1, FVC, PEF and MVV in group 3. However the improvement did not reach to the level of the healthy group (group 1) and still there is a significant difference in PFT between group 1 and group 3, as shown in Table 2. FEV1, FVC, PEF and MVV were all significantly decreased in group 3 after supplementation of vitamin D. Regarding FEV 1%, there was no significant differences between group 2 and 3. The difference in PFTs between group 1 and group 2 and 3 is a definitive result due to physical changes that characterized SCD patients. In addition, there may be changes in chest wall and vertebral structure among adults with SCD, which lead to the restrictive physiology [18]. This finding is consistent with what was reported by a prior study [21], which indicated the presence of abnormal respiratory function among SCD patients, and this could be as objective mark of chronic SCD and that PFT could be useful in management of the patients' signs and complications. Sickled erythrocytes induce endothelial injury and this initiates a series of reactions leading to pulmonary edema which may result in a fibrotic process and worsen the lung damage [22]. Therefore, fat embolism resulted from bone infarction, infections and intravascular clotting may contribute to the pulmonary hypertension [23].

Another important finding is the variation in the percentage of respiratory cases. When compared to the other groups (1 and 3), group 2 had the highest percentages of restrictive, obstructive, and combination cases (both restrictive and obstructive), and that the restrictive % was the highest compared to obstructive and combined cases. Vitamin D supplement, as in group 3 could reduce the high percentage of both mild and moderate instances, as well as the number of obstructive and mixed cases, while increasing the percentage of normal cases. A previous investigation was in line with this finding [21]. In addition to the restrictive lung functions pattern observed in SCD, an obstructive pattern also exists. Several prior studies revealed various abnormalities in PFT in SCD patients including restrictive and obstructive disease and hypoxemia [24-26]. Another probable pulmonary mechanism of restriction in the SCD patients is inadequate inspiration because of the chest pain resulting from peripheral vaso-occlusion, past rib infarctions, or a spinal condition [18].

The hematological profile showed significant differences in WBC, lymphocytes and granulocytes between group 1 and 2 and between group 1 and 3, but there was no significant differences between group 2 and 3. Despite the improvement in hematological parameters in group 3, it is still below the level of group 1, Additionally, we observed that patients with SCD in both groups (2 and 3) still exhibited elevated leucocyte counts in comparison to group 1, as shown in Table 3. In previous research, it has been found that SCD patients exhibit leukocytosis, abnormal activation of monocytes, granulocytes and endothelial cells, together with elevation in the level of multiple inflammatory mediators [27].

Regarding RBC, there were significant differences between group 1 and 2 and between group 1 and 3. No significant difference was found between group 2 and 3. We noted the same findings related to Hb and MCV, as seen in Table 2. These results agree with the findings of prior researches [27-29]. Chronic hemolytic anemia is a pathological feature of SCD in which there is increased lysis and adhesion of RBCs, and chronic hemolysis reduces the survival of RBC [30-31]. A published study suggested that low levels of Hb and HCT in SCD patients could be attributed to a poor response of erythropoietin connected with SCD. Interestingly, we observed in the present study

that MCH and MCHC showed improvement in their levels in group 3 compared to group 2, because of vitamin D supplement. Research has established that systemic or locally formed 1,25(OH)2D3 could be of a significant role in modulating cellular development such as hematopoiesis and differentiation. Therefore, vitamin D deficiency might have a negative impact on erythropoiesis in the bone marrow [14,32]. However, Soliman et al. found that deficiency of vitamin D did not have a significant effect either on RBC indices, WBC and their differential count [13]. Hence there are conflicted results about the effect of vitamin D on the hematological system.

Despite its name, vitamin D is a lipophilic nutrient that comes by diet or supplements, and is a hormone or prohormone that is essential for maintaining healthy bones and teeth. It also plays many other important roles in the body, including regulating inflammation and immune functions [33]. There have been numerous studies looking at the role of vitamin D in improving pulmonary functions. This effect may be due to its action on inflammatory regulation by its action on smooth muscles and on antimicrobial peptides, as well as in its help in limiting the complication of acute vaso-occlusive phenomena [34]. Moreover, vitamin D intake reduces inflammatory cytokines production through T-helper type 9 lymphocytes, such as interleukin-9 (IL9), (IL5) and (IL13) [35]. Furthermore, presence of vitamin D in type2 alveolar cells can stimulate the synthesis of surfactant and regulate the interactions of epithelial-mesenchymal tissue [36].

Recently, a number of studies have suggested that vitamin D could reduce oxidative stress and particulate matter-induced IL-6 response [37]. In addition, there is evidence for vitamin D having crucial action on the immune system, by elevating the levels of LL-37 (cathelicidin), which is a peptide capable of stimulating innate immunity and of damaging infectious agents [38]. What is more, some studies have linked vitamin D actions to restrained proliferation of metalloproteinases of the extracellular matrix (ECM), as well as the regulation of the synthesis to type III collagen by fibroblasts. Thus, the ECM of lung tissue plays an essential role in the pulmonary structures and mechanical properties, thus improving function [39].

In our work, the small number of patients involved in the study and not taking into account the number of crises in the patients' lives may be considered as limitation within the study, however, the presence of healthy people for comparison was of positivity and we could obtain information on the significant effect of vitamin D supplementation.

CONCLUSION

The findings of the present work indicated that supplementation of vitamin D in SCD patients could result in a relative improvement in lung function and reduce one of the potential consequences of the diseases.

DATA AVAILABILITY

The data used to support the findings of this study are included within the article.

CONFLICTS OF INTEREST

No conflicts of interest regarding the publication of this paper.

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