STATUS OF VITAMIN-D DEFICIENCY IN SICKLE CELL DISEASE IN ADULTS

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ABSTRACT

BACKGROUND

Sickle cell disease is a prevalent and a widely distributed disease in India. It has been found to be associated with multiple complications such as vaso-occlusion and painful crisis.

The aim of the study is to assess the status of vitamin D deficiency amongst adult SCD patients.

MATERIALS AND METHODS

A cross sectional study with appropriate control group was conducted amongst the patients of MY Hospital, Indore. The Sample included 50 cases and 50 controls. Selection of cases was done on the predefined criteria. The cases and controls were selected based on inclusion and exclusion criteria. The participants who consent to participate were included in the study. The information related to clinical, biochemical parameters were obtained from both the groups.

Statistical analysis was done using SPSS software. The comparison between the groups was done using Man Whitney U test, Chi square test and correlation was obtained using Spearman's correlation coefficient.

RESULTS

Results of the study showed presence of vitamin D insufficiency and deficiency amongst 92% of cases. The level of vitamin D showed significant correlation with frequency of painful crisis, blood transfusion and hospitalization.

CONCLUSION

It can be concluded that level of vitamin D decreases in SCD patients which can lead to complications such as painful crisis. So, vitamin D supplements can be given to such population to improve the condition of SCD patients.

KEYWORDS

Sickle Cell Disease, Vitamin D Deficiency, Painful Crisis, Blood Transfusion, Hospitalization.

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BACKGROUND

Sickle cell disease is a pro-inflammatory blood disorder having genetic inheritance which is commonly found in population of Indian, African, Arabian and origin.[1,2] It occurs due to mutation of beta chain globin gene of adult haemoglobin.[1] Haemoglobin S (HbS) was discovered by Linus Pauling and colleagues in 1949 and Vernon Ingram found abnormality in the amino acid sequence of the β-globin chain (β6Glu→Val) in sickle cell patients.[3] HbS gene in heterozygous state is usually harmless but homozygous HbS gene exhibit itself in a severe condition resulting in destruction of red blood cells which may lead to blockage of blood vessel thus hampering blood flow and ultimately leading to painful and often serious complications such as stroke, acute chest syndrome, acute and chronic bone complications, including painful vaso-occlusive crisis, osteomyelitis, osteonecrosis & osteoporosis.[1, 2] Due to vaso-occlusion downstream tissues get deprived of nutrients and oxygen which results in ischemia and death of tissue.[4] Patients with Sickle Cell Anaemia have increased risk of vitamin-D deficiency.[5] Vitamin D is important for calcium metabolism which in turn is important for bone metabolism. Calcium deficiency causes reduction in the ideal bone mass peak in children and adolescents with sickle-cell anaemia leading to growth failure. Vitamin D deficiency is also associated with increased muscle weakness, respiratory infections, and increased tendency of falls and microlesions. Vitamin D deficiency may worsen bone condition in children with sickle-cell anemia.[6] The bone mineral density of the patients with sickle cell disease was found to be less and improvement was observed after vitamin D supplementation.[7]

Metabolism of Vitamin D is complex and requires homeostasis between different organ systems, including the parathyroid gland, skin, intestines, liver and kidney. There are many characteristics which are specific to Sickle cell disease which may contribute to Vitamin D deficiency.[8] Few of these characteristics are reduced appetite, there is inadequate absorption of nutrients because of damage to intestinal mucosa,[9] to compensate for rapid destruction of RBCs, there is continuous production of RBC and thus basal

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metabolic rate of such persons is more with higher nutritional demands so as to maintain normal physiologic functioning.[8] Persons with sickle cell disease may have renal pathology secondary to their haematological disease which may reduce conversion of vitamin D to its active form. Sickle cell disease is an inflammatory condition and the level of vitamin D binding protein declines in inflammatory conditions.[8]

Prevalence of vitamin D deficiency among individuals with Sickle Cell Disease has been reported to be 33% to 100%.[2] Prevalence of Vitamin D deficiency in study population was found to be 98% amongst patients of sickle cell disease patients at 2 medical centers in United states.[1]

Aim

To assess the status of vitamin -D deficiency amongst adult SCD patients.

Objectives

- To assess the status of vitamin D deficiency amongst adult SCD patients and to compare with those not suffering from SCD.
- To assess any association between painful crisis and severity of Vitamin D deficiency amongst SCD patients.
- To assess any association between frequency of blood transfusion and severity of Vitamin D deficiency amongst SCD patients.
- To assess any association between frequency of hospitalization and severity of Vitamin D deficiency amongst SCD patients.

Research Hypothesis

- Null hypothesis – The prevalence of vitamin D deficiency does not differ amongst those having SCD and not having SCD and there is no association between Vitamin D deficiency and episodes of painful crisis, frequency of blood transfusion and hospitalization.
- Alternate hypothesis- The prevalence of vitamin D deficiency is high amongst those having SCD as compared to those not having SCD and there is an association between Vitamin D deficiency and episodes of painful crisis, frequency of blood transfusion and hospitalization.

MATERIALS AND METHODS

A cross sectional study with appropriate control group was carried out. Study sample consisted of 100 participants divided into two groups – case and control. Sample was drawn from the patients visiting Department of General medicine of Mahatma Gandhi Medical College and Hospital, Indore. Study was conducted for duration of 1 year from March 2017 to March 2018. Informed and written consent was obtained from the participants. Participants were selected on the basis of inclusion and exclusion criteria. Inclusion criteria were diagnosed sickle cell disease patients, age group- above 12 years. Exclusion criteria were prisoners, mentally ill patients, patients not giving consent, patient with renal disease, already on Vitamin D therapy. Diagnosis was made on the basis of history, presence of clinical symptoms, physical examination and laboratory examination. (Table 1).

Information Obtained	
History	Personal information such as name, age, gender, weight, marital status, occupation.
	Disease related history
Clinical signs & symptoms	Feeling of tiredness and weakness, pain including chest pain, shortness of breath and/or dizziness, headache, coldness in hands& feet, pale skin due to anaemia, jaundice or yellow eyes and skin, leg ulcer that do not heal,
Physical examination	Pulse using Stethoscope, blood pressure using sphygmomanometer, weight using weighing machine, height using stadiometer, Body Mass Index.
Laboratory examination	Total and differential leukocyte count - Automated Cell Counter Analyzer& confirmed by manual oil immersion smear study method.
	RBC counting and RBC parameters Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Packed Cell Volume (PCV) & Red blood cell distribution width (RDW) - automated cell counter analyser.
	Platelet count - Automated Cell Counter Analyzer & confirmed by manual oil immersion smear study method.
	Total bilirubin was done by the method based on coupling reaction with various diazo dyes.
	Albumin concentration using immunochemical method.
	Serum Aspartate amino Transferase concentration by IFCC without PSP.
	Serum Alanine Transaminase concentration by IFCC without PSP.
	Reticulocyte count
	Lactate Dehydrogenase concentration using automated colorimetric method.
	Vitamin D level by Liaison method.
	Sickle cell RBC using electrophoretic method.

Table 1. Information Obtained from the Study Participants.

The data obtained was analysed using Statistical package for the social sciences (IBM SPSS Statistics 20.0). Descriptive statistics was used to know the frequency of study subjects within various categories and to calculate the mean and standard deviation of continuous data. Normality of data was assessed using Kolmogorov-Smirnoff or Shapiro-Wilk test. Inter-group comparison was done using chi square test and appropriate parametric or non-parametric test. Association between different parameters was assessed using correlation coefficients. p value < 0.05 was considered statistically significant. Confidence interval was set at 95%.

Ethical Clearance-

Ethical clearance was obtained from the research committee of MGM College and MYH hospital, Indore (M.P.).

RESULTS

The description of various parameters included in the study and the comparison of group A and B based on those parameters have been described in Table 2 & 3.

Parameter	Group A			Group B			p value
	Mean	Standard Deviation	Median	Mean	Standard Deviation	Median	
Age (in years)	21.02	4.64007	20.0000	21.36	4.62804	20.5000	0.748
Haemoglobin (g/dl)	8.8680	1.47281	9.0000	13.6360	0.82654	13.9000	0.000*
Haematocrit (%)	26.4880	3.83319	27.0000	45.8800	1.70999	46.0000	0.000*
Platelet	2.0796	1.01973	1.9000	2.8814	0.38188	2.9000	0.000*
Reticulocyte count	1.1400	0.40457	1.0000	0.9920	0.15365	1.0000	1.000
Serum creatinine concentration (mg/dl)	1.4350	5.16147	0.6200	0.7346	0.08995	0.7600	0.001*
Serum Urea concentration (mg/dl)	27.9100	27.50032	21.0000	15.1560	2.63231	15.0000	0.001*
Serum Bilirubin (mg/dl)	3.4192	3.26449	2.6700	0.6348	0.13556	0.6000	0.000*
SGOT (U/L)	57.8820	37.30917	47.5000	26.3400	4.86390	24.0000	0.000*
SGPT (U/L)	39.0940	23.16411	34.0000	29.7400	5.97208	30.0000	0.057
Serum LDH (U/L)	751.4200	485.42151	653.50000	150.8600	21.20936	149.0000	0.000*
Serum alkaline phosphatase	181.2800	102.46912	158.0000	81.1800	9.99120	79.5000	0.000*
Serum vitamin D (ng/ml)	13.1446	9.11059	11.5000	32.5900	6.91468	35.5000	0.000*

Table 2. Description and Comparison of Group A and B based on Various Parameters Included in the Study

Parameter		Group A	Group B	p value∞
Gender	Male	27	27	-
	Female	23	23	
Haemoglobin concentration	Low (<12 mg/dl for females, < 14 mg/dl for males)	49	5	0.000*
	Normal (12-14 mg/dl for females, 14-16 mg/dl for males)	1	45	
	High (>more than 14 mg/dl for females, >16 mg/dl for males)	0	0	
Haematocrit	Low (<38.8% for males, <35.4% for females)	50	0	0.000*
	Normal (38.8 to 46.4 for males, 35.4 to 44.4 for females)	0	18	
	High (> 46.4 for males, >35.4 to 44.4 for females)	0	32	
Platelet count	Low (<1.65 lakhs/cubic mm)	19	0	0.000*
	Normal (1.65 to 4.15 lakhs/cubic mm)	31	50	
	High (> 4.15 lakhs/cubic mm)	0	0	
Creatinine concentration	Low (<0.5 mg/dl for females, <0.6 mg/dl for males)	24	0	0.000*
	Normal (0.5 to 0.9 mg/dl for females, 0.6 to 1.2 mg/dl for males)	23	50	

	High (>0.9 mg/dl for females and 1.2 mg/dl for males)	3	0	
Blood urea level	Low (<10 mg/dl)	0	0	0.059
	Normal (10-50 mg/dl)	46	50	
	High (>50 mg/dl)	4	0	
Bilirubin level	Low (<0.3mg/dl)	0	0	0.000*
	Normal (0.3- 1.3mg/dl)	7	50	
	High (>1.3 mg/dl)	43	0	
SGOT	Low (<12 U/L)	0	0	0.000*
	Normal (12 to 38 U/L)	15	5	
	High (>38 U/L)	35	0	
SGPT	Low (<7 U/L)	0	0	0.011*
	Normal (7 to 41 U/L)	32	43	
	High (>41 U/L)	18	7	
LDH	Low (<115 U/L)	0	0	0.000*
	Normal (115-221 U/L)	0	50	
	High (221 U/L)	50	0	
Reticulocyte count	Low (<0.8% for females, <0.8% for males)	4	3	0.659
	Normal (0.8-2.0% for females, 0.8 to 2.3% for males)	46	47	
	High (>2.0% for females, >2.3% for males)	0	0	
Alkaline phosphatase	Low (< 65 U/L)	0	0	0.000*
	Normal (65 to 306 U/L)	12	50	
	High (>306 U/L)	38	0	
Vitamin D	Sufficient (≥ 30 ng/ml)	4	30	0.000*
	Insufficient (20 to 29.9 ng/ml)	4	20	
	Deficiency (<20 ng/ml)	20	0	
	Severe deficiency (<10 ng/ml)	22	0	

Table 3. Comparison of Group A and B based on Frequency Distribution of Participants based on Parameters included in the Study

∞ Chi-square test

Haemoglobin concentration, haematocrit value and platelet count of SCD patients was significantly less than that of controls. The creatinine concentration was also found to be significantly less in cases as compared to controls. However, Serum Urea concentration, Serum Bilirubin, SGOT, Serum LDH, Serum alkaline phosphatase was significantly more amongst cases as compared to control.

Serum vitamin D level was significantly less in SCD patients as compared to controls. Number of subjects with low haemoglobin concentration was significantly more in group A (88%). Sixty two percent patients in group A had normal platelet count whereas in group B 100% had normal platelet count and thus two groups differ significantly based on number of individuals with low and normal count. The two were significantly different with respect to the number of participants with low and normal creatinine concentration. The number of individuals with low creatinine concentration was significantly greater in group A. The group A & B participants were having non-significant difference in blood urea level (p value >0.05). In both groups the maximum patients reported normal blood urea level. Haematocrit value was low in all the individuals in group A, on the contrary no participant in group B had low haematocrit value. The two groups differ significantly based on the number of individuals with low, normal and high haematocrit value ($p<0.05$). Bilirubin level was normal in all the participants in group B but only 14% patients had normal bilirubin level in group A and maximum had high bilirubin. The number of patients with normal bilirubin was significantly less in group A and with high bilirubin was significantly high. The number of patients with normal SGOT was significantly high in group B and significantly less in group A (30%) and vice versa. Similar to SGOT, neither in group A nor in group B any patient reported with low SGPT. In group B, maximum patients 86% had normal SGPT. All patients of SCD reported with high LDH concentration, whereas, the number of patients with low and normal LDH concentration was significantly high in group B. Only 8% individuals in group A and 6% individuals in group B had low Reticulocyte count, this difference was not statistically significant. The number of individuals with normal alkaline phosphatase level was significantly high in group B than group A and the number of participants with high alkaline phosphatase level was significantly high in group A than group B. The maximum (44%) patients in group A were found to have severe vitamin D deficiency, 40% were Vitamin D deficient, 8% had insufficient vitamin D and 8% had sufficient Vitamin D. The number of patients having Vitamin D deficiency was

significantly more in group A and number of patients with sufficient and insufficient but not deficient was significantly more in group B.

Platelet count, bilirubin concentration, SGOT, SGPT, LDH and alkaline phosphate also showed negative correlation with vitamin D concentration. With the increase in Platelet count, bilirubin concentration, SGOT, SGPT, LDH and alkaline phosphate concentration, a decrease in vitamin D level was noticed. This negative correlation was statistically significant between bilirubin concentration and vitamin D. Alkaline phosphatase also showed statistically significant correlation. A significant decrease in vitamin D concentration was found with the increase in urea concentration. Haemoglobin concentration, haematocrit value, reticulocyte count and vitamin D had no significant correlation.

Vitamin D		
	Spearman Correlation Coefficient	**p value**
Age	-0.032	0.823
Haemoglobin Concentration	0.224	0.118
Platelet Count	-0.343	0.015*
Creatinine Concentration	0.273	0.055
Urea Concentration	0.305	0.031*
Haematocrit Value	0.130	0.368
Bilirubin Concentration	-0.231	0.170
SGOT	-0.180	0.211
SGPT	-0.282	0.047
LDH	-0.020	0.888
Reticulocyte Count	0.149	0.301
Alkaline Phosphatase	-0.298	0.036*

Table 4. Correlation between Vitamin D and Age, Haemoglobin Concentration, Platelet Count, Creatinine Concentration, Urea Concentration, Haematocrit Value, Bilirubin Concentration, SGOT, SGPT, LDH, Reticulocyte Count, Alkaline Phosphatase

*p value < 0.05 was considered statistically significant.

A significant association was observed between vitamin D concentration and painful crisis. Maximum number of episodes of painful crisis reported were 4 episodes per year and such high frequency was seen amongst the patients with severe vitamin D deficiency. The frequency of 3 episodes of painful crisis per year was observed in patients with deficient vitamin D concentration. The patients with insufficient vitamin D concentration experienced less frequent episodes of painful crisis. (Table-5)

		Pain frequency				**p Value**
		1 or Less than 1 Per Year	**2 Per Year**	**3 Per Year**	**4 Per Year**	
Vitamin D concentration	Sufficient	4	0	0	0	0.000*
	Insufficient	0	4	0	0	
	Deficiency	0	0	20	0	
	Severe deficiency	0	0	0	22	
	Total	4	4	20	22	

Table 5. Association between Vitamin D Concentration and Pain Crisis in the Participants of Group A

*p value < 0.05 was considered statistically significant.

A highly significant association was observed between frequency of hospitalization and vitamin D deficiency. Patients with severe vitamin D deficiency and deficiency visited hospital significantly more than those with insufficient and sufficient vitamin D level. (Table -6)

		Frequency of Hospitalization			
		Less than 1 in a Year	**1 in a Year**	**More than 1 in a Year**	**p Value**
Vitamin D concentration	Sufficient	4	0	0	0.000*
	Insufficient	0	4	0	
	Deficiency	0	3	17	

	Severe deficiency	0	0	22	
	Total	4	7	39	

Table 6. Association between Vitamin D Concentration and Frequency of Hospitalization in the Participants of Group A

*p value < 0.05 was considered statistically significant.

Similarly, frequency of blood transfusion also shows significant association with vitamin D deficiency. History of blood transfusion was significantly high with deficient vitamin D. Most of the patients had 1 time blood transfusion in a year. (Table-7).

		Frequency of Blood Transfusion			
		Less than 1 in a Year	**1 in a Year**	**More than 1 in a Year**	**p Value**
Vitamin D concentration	Sufficient	4	0	0	0.000*
	Insufficient	4	0	0	
	Deficiency	3	17	0	
	Severe deficiency	0	17	5	
	Total	11	34	5	

Table 7. Association between Vitamin D Concentration and Blood Transfusion in Participants of Group A

*p value < 0.05 was considered statistically significant.

DISCUSSION

In the present study the mean & median vitamin D concentration (13.1446 ng/ml & 11.5000 ng/ml respectively) was significantly less than the mean and median vitamin D concentration in control group (32.5900 ng/ml & 35.5000 ng/ml).

According to the criteria of vitamin D deficiency followed in our study, the prevalence of severe vitamin D deficiency was 44% and vitamin D deficiency was 40%, combinedly the prevalence of Vitamin D deficiency was 84%. Considering for insufficient Vitamin D level, the 92% SCD patients were found to be affected. Goodman III et al., (2010) studied the prevalence of vitamin D deficiency in sickle cell disease patients in United States. They also reported high prevalence of vitamin deficiency amongst SCD patient. They found 60% individuals to be severely vitamin D deficient and vitamin D level was suboptimal (<30 ng/ml) in 98% individuals.[10] Our study also reported insufficient Vitamin D level in 92% SCD patients.

In the present study, the platelet count amongst SCD patients was significantly less as compared to those not suffering from SCD. Jain D et al., (2017) reported significantly increased vaso-occlusive crisis amongst children having SCD, which may be indicating towards decreased platelet count.[11] Shanley et al., (2011) also studied the usefulness of platelet count as a predictor of VOC amongst SCD patients and reported larger decline in platelets count in them.[12] Shome DK et al., (2018) suggested the mechanism to explain alteration in platelet count in SCD. They suggested that direct correlations of platelet counts with WBC and reticulocytes found in their study suggest that compromised marrow function is a contributory factor. Compromised marrow function could be because of vaso-occlusive marrow infarction or sepsis. Also, sickle cell-endothelial interaction results in coagulation factor activation and a state of compensated disseminated intravascular coagulation with platelet consumption.[13]

The median Serum creatinine level reported in the study was 0.6200 mg/dl in group A participants and 0.7600 mg/dl amongst group B participants. The range varied from 0.50 to 0.90 mg/dl in control group. Mascha Verma et al., calculated reference interval for serum creatinine to be 0.40 to 1.3 mg/dl.[14] In the present study, all the participants of group B had normal level of creatinine. Whereas in group A almost 48% patients had low creatinine level and 46% had normal creatinine concentration. GB Silva Junior et al., (2012) studied renal function in SCD. They also reported a low level of creatinine in young patients. The present study was also done on young patients, the young age could be also be the possible explanation of low creatinine level.[15]

A negative correlation was obtained between age and vitamin D level suggesting that with increasing age, vitamin D concentration decreases. Similar findings were reported by Zhu et al., (2012) who found that serum 25 - hydroxyvitamin D levels among paediatric population decreased when the children became older, and the prevalence of vitamin D deficiency increased at the same time.[11] Holick MF (1995) reported that the vitamin D synthesis within the body decreases with aging. Although in the present study, this association was not found to be statistically significant.[16]

In the present study, a significant association was found between frequency of blood transfusion and severity of vitamin D deficiency. Also, significant association was observed between frequency of hospitalization and severity of vitamin D deficiency. Similar findings were reported by Jain D et al., (2017), they found increased blood transfusion and hospitalization has significant association with vitamin D deficiency.[12]

CONCLUSION

Vitamin D deficiency correlated with severity of SCD as indicated by clinical parameters such as frequency of painful crisis, hospitalization and blood transfusion. This correlation was also evident with other biochemical parameters such as increased alkaline phosphatase, low platelet count.

Further research with adequate sample size is needed to further evaluate these correlations.

The results of study indicate that vitamin D can be given to SCD population to improve the condition of SCD patients. Further studies are needed to evaluate the effect of vitamin D supplementation in clinical and biochemical parameters.

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