

Original Research Article

A study of Vitamin D deficiency in patients of sickle cell disease and its association with severity

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ABSTRACT

Background: Both SCD and Vit. D deficiency may cause joint pain. So, Vit. D may have a contributory role in severity of SCD presentation. This study was performed to assess burden of Vitamin D levels and association of vitamin D deficiency with severity of SCD in a tertiary care centre in India.

Methods: This was a cross-sectional study, performed for one and half year. All SCD patients >18 years of age were included. Data was analysed to assess the burden of Vitamin D deficiency and to find out any correlation of S. vitamin D level with anemia, jaundice and number of episodes of hospital admissions in patients of SCD.

Results: Total 50 patients were included. Multiple joint pain and easy fatigability were the most common symptoms. Most of them had history of jaundice and anaemia in the past, 84% had Vitamin D deficiency. There was significant difference in values of serum total bilirubin, blood urea, SGPT, SGOT, HbF, HbA2 and haemoglobin between the patients with Vitamin D3<30 and vitamin D3≥30 (p<0.05). There was a significant positive correlation of vitamin D3 with haemoglobin (r = 0.889) and a negative correlation with Hb A2 (r= -0.123) and total bilirubin (r= -0.438).

Conclusions: Vitamin D3 deficiency is associated with increased morbidity in SCD in terms of joint pain, anemia and jaundice. Routine testing and supplementation of Vitamin D levels in these patients may help to alleviate pain, improve functionality and reduce complications.

Keywords: Anemia, Jaundice, Severity, Sickle cell disease, Vitamin D deficiency

INTRODUCTION

Sickle cell disease (SCD) is a genetic disorder with various life threatening organ-system complications like recurrent painful vaso-occlusive crises, hemolytic anemia, jaundice, infarcts and acute chest syndrome.¹ Globally seen in three lakh births annually, it is highly prevalent in central and western India.² ICMR has reported that 30% children with SCD die before reaching adulthood and that mortality by the age of two in children with SCD is 20 %.^{3,4} Over a billion people worldwide have vitamin D deficiency which has also been reported to be highly prevalent with sickle cell haemoglobinopathy.⁵⁻⁷ As both SCD and Vit. D

deficiency may cause joint pain, Vit. D may have a contributory role in severity of SCD presentation.

Hence, this study was done to assess correlation of vitamin D level with anemia, jaundice and number of episodes of hospital admissions in SCD patients.

METHODS

This was a cross-sectional study conducted in medicine department of a tertiary care hospital on western coast of Gujarat. The study was started after obtaining clearance from Institutional Ethical Committee and was carried out for one and a half year from January 2017.

All patients >18 years of age coming to Medicine OPD or admitted in wards and diagnosed as sickle cell disease on hemoglobin electrophoresis were enrolled in the study. Only those who gave written informed consent for participation in the study were included. Patients already on vitamin D supplements and known cases of chronic kidney disease, chronic liver disease and anemia of other etiology were excluded from the study.

Minimum sample size of 38 was calculated according to the below formula, however the patients who came after this number was achieved, till one and a half year after start of the study were also included.

$$n = \frac{Z^2 P(100-P)}{d^2}$$

where;

n=Sample size with finite population correction

Z=1.96 [Z statistic for level of confidence]

P=75 [Expected prevalence] and

d=precision [20% of prevalence]

Detailed history regarding symptoms, number of previous admissions in last one year and number of pain crisis in last one year was taken from of all participants. Any history of anemia, chronic kidney disease, chronic liver disease or jaundice in the past year was also noted. All cases were subjected to CBC (complete blood count), RFT (renal function tests), LFT (Liver function tests), Sickling, Hemoglobin electrophoresis and Vitamin D level. ECG, Chest X ray, USG abdomen, 2D Echo and other specific investigations were done as per indication.

Sickling test was done by dithionate qualitative solubility test. Haemoglobin electrophoresis was done in BIO-RAD D-10 DUAL PROGRAM machine. The D-10 Dual Program is based on chromatographic separation of the analytes by ion exchange high performance liquid chromatography (HPLC).

Haemoglobin phenotype was confirmed by a high-pressure liquid chromatography hemoglobin fractionation method. Serum Vitamin D level was measured by Chemiluminescence-immuno Assay (CLIA) Method in Access 2 model machine by Beckman Coulter. Vitamin D level below 30 ng/ml was considered deficient while Vitamin D level above and equal to 30 ng/ml was considered normal.

Main outcome and measures: Data was analysed to assess the burden of Vitamin D deficiency in patients of sickle cell disease. Odd's ratio was calculated to find out if there was any association between vitamin D deficiency and anemia or jaundice or hospital admission rate. Pearson's correlation coefficient was measured to find out any correlation of S. vitamin D level with hemoglobin, bilirubin, liver enzymes or number of hospital admissions in the previous year.

RESULTS

Total 50 patients of sickle cell disease were included. >95% of the patients were <40 years in age. Nine patients (18.00%) were below 20 years, 35 patients (70.00%) were in the age group of 21 - 30 years, while four (8.00%) were in 31 - 40 years age group. Only two patients (4.00%) were more than 40 years in age. 33 (66.00%) were males and 17 (34.00%) were females.

Most common presenting complaint was multiple joint pain, seen in 39 patients (78.00%) followed by easy fatigability (72.00%), fever (68.00%), jaundice (50.00%), abdominal pain (24.00%), breathlessness (14.00%) and cough (6%). Hence, the most common complaints were multiple joint pain, easy fatigability and fever. Most common signs were pallor and icterus seen in 41 (82.00%) and 25 (50.00%) patients respectively. None of the study participants had cyanosis, clubbing, lymphadenopathy or oedema. Mean Hb was 8.62±1.95 g/dL, mean HBs was 69.44±8.31%, mean HbA2 was 3.18±0.87% and mean HbF was 15.54±5.37%. Mean value of Vit D was 22.84±5.61 ng/ml. Mean of total count, platelet count, blood urea and S. creatinine were within normal limits. (10890±5286.19 cells per cu mm, 2.31±1.16 X 10⁵ cells per cu mm, 31.04±16.17 mg/dL and 1.06±0.24 mg/dL respectively). The median value of total bilirubin was 3 mg/dl whereas the median values of SGPT and SGOT were 34.5 IU/L and 39.5 IU/L respectively.

Total 42 (84.00%) patients had vitamin D level below 30 ng/ml with the mean value of 21.05±4.09 ng/ml while eight (16.00%) patients had vitamin D levels more than 30 ng/ml with mean Vitamin D3 level 32.25±1.39 ng/ml; the difference being statistically significant (p<0.05). Haemoglobin in patients with vitamin D3 <30 ng/ml was 8.14±1.73 g/dl as compared to 11.13±0.64 g/dl in the other group (vitamin D3≥30); the difference was statistically significant (p=0.000). A statistically significant difference between the SCD patients with or without vitamin D deficiency was also seen in s. bilirubin (5.19±6.45 mg/dl as compared to 1.63±1.06 mg/dl; p=0.002), serum creatinine (1.05±0.22 mg/dl as compared to 1.13±0.35mg/dl; p=0.566) and blood urea (32.88±16.88 mg/dL as compared to 21.38±5.85 mg/dL; p=0.002).

Similarly there was a significant difference between the two groups in terms of values of SGPT (60.48±63.01IU/L as compared to 27.38±19.01IU/L; p=0.008), SGOT (74.24±93.88 IU/L as compared to 35.25±23.13 IU/L; p=0.024), HbF (15.19±5.55% as compared to 18.25±3.41%; p=0.045) and HbA2 (3.29±0.89% as compared to 2.63±0.52%; p=0.011). Thus, it was observed that there was significant difference in values of serum total bilirubin, blood urea, SGPT, SGOT, HbF, HbA2 and haemoglobin between the two groups with Vitamin D3 <30 ng/ml and vitamin D3≥30 ng/ml (Table 1).

Table 1: Difference in lab reports of patients with or without Vitamin D deficiency.

Parameter	Vit D3 < 30			Vit D3 ≥ 30			p value
	Mean	SD	SE	Mean	SD	SE	
Total Bilirubin (mg/dl)	5.19	6.45	1.00	1.63	1.06	0.38	0.002
S. Creatinine (mg/dl)	1.05	0.22	0.03	1.13	0.35	0.13	0.566
Blood Urea (mg/dl)	32.88	16.88	2.60	21.38	5.85	2.07	0.002
SGPT	60.48	63.01	9.72	27.38	19.01	6.72	0.008
SGOT	74.24	93.88	14.49	35.25	23.13	8.18	0.024
HBS (%)	69.71	8.70	1.34	68.00	6.09	2.15	0.511
HbF (%)	15.02	5.55	0.86	18.25	3.41	1.21	0.045
HbA2 (%)	3.29	0.89	0.14	2.63	0.52	0.18	0.011
PC /cu.mm	2.25	1.18	0.18	2.63	1.06	0.38	0.391
TC /cu.mm	10985.71	5529.28	853.19	10387.50	4024.01	1422.70	0.724
Hb (mg/dl)	8.14	1.73	0.27	11.13	0.64	0.23	0.000

Table 2: Odds of altered bilirubin in SCD patients with or without Vitamin D deficiency.

Vitamin D3	Bilirubin				Total	Odds ratio	p value
	>1.2	%	<1.2	%			
<30	38	90.48%	4	9.52%	42	9.500	0.016
≥30	4	50.00%	4	50.00%	8		
Total	25	50.00%	25	50.00%	50		

Table 3: Odds of anemia in SCD patients with or without Vitamin D deficiency.

Vitamin D3	Hb (mg%)				Total	Odds ratio	p value
	<8	%	>8	%			
<30	25	59.52%	17	40.48%	42	24.770	0.004
≥30	0	0.00%	8	100.00%	8		
Total	25	50.00%	25	50.00%	50		

Table 4: Correlation of Vitamin D level with other blood investigations.

Parameter	Unstandardized coefficients		Standardized coefficients	Pearson coefficient	T	p value
	B	Std. Error	Beta			
(Constant)	-2.177	7.132			-0.305	0.762
Hb (mg %)	2.44	0.25	0.85	0.889	9.63	0.000
TC (/cu.mm)	0.00	0.00	0.07	-0.072	0.93	0.359
PC (/cu.mm)	-0.29	0.39	-0.06	0.312	-0.75	0.461
HBs (%)	-0.06	0.08	-0.09	-0.044	-0.77	0.447
HbA2 (%)	1.19	0.55	0.19	-0.123	2.16	0.037
HbF (%)	0.13	0.09	0.13	0.270	1.55	0.129
B. Urea (mg/dl)	-0.01	0.03	-0.03	-0.233	-0.34	0.734
S. Creatinine (mg/dl)	3.21	1.90	0.14	0.053	1.69	0.099
T. Bilirubin (mg/dl)	-0.19	0.08	-0.20	-0.438	-2.20	0.034
SGPT (U/L)	0.00	0.02	0.03	-0.211	0.15	0.881
SGOT (U/L)	0.00	0.01	-0.07	-0.111	-0.37	0.713

Since there was a significant difference in values of haemoglobin, bilirubin, SGPT, SGOT, urea, HbF and HbA2, Odds ratio (OR) was calculated to find if there was any association between vitamin D deficiency in

SCD patients and anemia, jaundice, elevated liver enzymes or altered HbF or HbA2 levels.

It was found that there were 9.5 times odds of S. bilirubin being >1.2 mg/dl versus <1.2 mg/dl in patients of vitamin

D3 <30ng/ml IU versus >30 ng/ml (p value= 0.016) (Table 2), 24 times odds of Hb being < 8.0 g/dl versus >8.0 g/dl in patients of vitamin D3 <30 ng/ml versus >30 ng/ml (p=0.004) (Table 3).

Thus, there was a significant association of vitamin D deficiency with anemia and jaundice in patients of SCD. It was found that there were three times odds of episodes of hospitalization in past one year in patients of vitamin D3 <30 ng/ml versus >30 ng/ml, however, this value was not statistically significant (p value=0.307).

On assessing the correlation between vitamin D deficiency in SCD and values of hemoglobin, bilirubin, SGOT, SGPT, blood urea, HbF and HbA2, it was found that there was a positive correlation of vitamin D value with values of haemoglobin and HbF (Pearson correlation coefficient $r = 0.889$; $p=0.000$ and 0.270 ; $p=0.129$, respectively). Thus, there was a significant positive correlation of Vitamin D with haemoglobin level but the correlation with HbF was weak (Table 4).

Authors also found a mild negative correlation of Vitamin D value with values of total leukocyte count, HbS, HbA2, urea, total bilirubin, SGPT and SGOT but the correlation was not significant with any of these parameters.

DISCUSSION

The most common age group of SCD patients in the present study was 21 to 30 years, similar to that reported previously in India.⁸ Approximately, two third of the patient population was males, which may be due to the fact that, in India there is lower healthcare utilization rate among females.⁹

There is high prevalence of Vitamin D deficiency in India which has been reported to prevail in children and adults with SCD also.^{10,11} Statistically 84% of the SCD patients in our study were found to have vitamin D insufficiency similar to the previously reported.^{12,13} The lower vitamin D levels have been reported to be associated with both chronic and acute pain as well as with higher opioid usage in sickle cell patients.¹⁴⁻¹⁶ In the present study 78% and 72% of the patients complained of multiple joint pain and easy fatigability respectively, which was more commonly seen in vitamin D deficient population.

Low vitamin D level in patients with SCD has been attributed by some to high incidence of renal impairment.¹³ Guasch et al, showed that 70% of adults with HbSS disease and 40% with other sickling disorders had some degree of glomerular involvement and the incidence increases with age.¹⁷ Adla et al, proved that renal insufficiency defined by glomerular filtration rate (GFR) <90 ml/min was present in 21% of the SCD subjects and an estimated GFR of <60 ml/min was found to be a predictor of vitamin D deficiency.¹⁸ However, we did not find any significant renal involvement in our

study population, so we cannot attribute association vitamin D deficiency seen in our patients to renal insufficiency.

Liver enzymes were significantly higher among SCD patients with vitamin D insufficiency as in another study which found that SCD subjects with vitamin D level <50nmol/L were more prone to vaso-occlusive crisis and had significantly higher levels of total bilirubin and conjugated bilirubin when compared with those who had ≥ 50 nmol/L vitamin D level.¹⁹

Few researchers have studied effect of vitamin D supplementation in patients with sickle-cell disease. Osunkwo et al, supplemented 46 subjects with sickle-cell anemia with 500 mg of calcium and 200 IU of vitamin D for a period of 6 months, and observed lesser pain and lower incidence of painful crises.¹⁵

In the study by Shams et al, children with sickle-cell anemia received daily supplementation of 400 IU of vitamin D for a period of 6 months and found a lower incidence of complications associated with sickle-cell anemia, as well as less need for analgesia.²⁰ However, we did not study effect of supplementation of vitamin D in this study. Thus, findings of this study support the evidence that there is significant vitamin D deficiency in patients of SCD and that acute and chronic pain as well as anemia, jaundice and number of hospital admissions are more frequently seen in vitamin D deficient subset of SCD patients.

CONCLUSION

Authors recommend routine testing of serum vitamin D levels in SCD patients and accordingly supplement the same to alleviate pain, improve functionality, reduce development of anemia and jaundice and reduce requirement of hospital admission in those with vitamin D insufficiency. A multicentric randomized controlled study will help in elucidating the overall impact of vitamin D supplementation on the clinical outcome in SCD patients.

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REFERENCES

1. Bender MA. Sickle Cell Disease. 2003 Sep 15 [Updated 2017 Aug 17]. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. University of Washington, Seattle;1993-2020.
2. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet*. 2013;381(9861):142-51.

3. Tewari S, Rees D. Morbidity pattern of sickle cell disease in India: A single centre perspective. *Ind J Med Res.* 2013;138(3):288.
4. Rupani MP, Vasava BC, Mallick KH, Gharat VV, Bansal R. Reaching community through school going children for sickle cell disease in Zankhvav village of Surat district, Western India. *Online J Health Allied Sci.* 2012;25(11): 2-4.
5. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357(3):266-81.
6. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *The Am J Clinical Nutr.* 2008;87(4):1080S-6S.
7. Jackson TC, Krauss MJ, DeBaun MR, Strunk RC, Arbeláez AM. Vitamin D deficiency and comorbidities in children with sickle cell anemia. *Pediatr Hematol Oncol.* 2012;29(3):261-6.
8. Kamble Á, Chaturvedi P. Epidemiology of sickle cell disease in a rural hospital of central India. *Indian Pediatr.* 2000;37(4):391-6.
9. Nair H, Campbell H, Park JJ, Brondi L, Shi T, Olsson S. Common childhood infections and gender inequalities: a systematic review. *UNICEF Maternal, Newborn and Child Health Working Papers.* New York; 2015.
10. Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. *Nutr.* 2014;6(2):729-7.
11. Rovner AJ, Stallings VA, Kawchak DA, Schall JI, Ohene-Frempong K, Zemel BS. High risk of vitamin D deficiency in children with sickle cell disease. *J Am Dietetic Assoc.* 2008;108(9):1512-6.
12. Goodman III BM, Artz N, Radford B, Chen IA. Prevalence of vitamin D deficiency in adults with sickle cell disease. *J Nat Med Assoc.* 2010;102(4):332-5.
13. Nolan VG, Nottage KA, Cole EW, Hankins JS, Gurney JG. Prevalence of vitamin D deficiency in sickle cell disease: a systematic review. *PLoS One.* 2015;10(3):e0119908.
14. Osunkwo I, Hodgman EI, Cherry K, Dampier C, Eckman J, Ziegler TR, et al. Vitamin D deficiency and chronic pain in sickle cell disease. *Brit J Haematol.* 2011;153(4):538-40.
15. Lee MT, Licursi M, McMahon DJ. Vitamin D deficiency and acute vaso-occlusive complications in children with sickle cell disease. *Pediatr Blood Cancer.* 2015;62(4):643-7.
16. Han J, Saraf SL, Zhang X, Gowhari M, Molokie RE, Hassan J, et al. Patterns of opioid use in sickle cell disease. *Am J Hematol.* 2016;91(11):1102-6.
17. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. *J Am Soc Nephrol.* 2006;17(8):2228-35.
18. Hassan AB, Garadah TS, Jaradadat AA, Ajmi A, Alawi ME, Sequeira RP. Prevalence of vitamin D deficiency in patients with sickle cell disease in Bahrai Intl. *J Med.* 2013;1:23-8.
19. Akinlade KS, Atere AD, Rahamon SK, Olaniyi JA, Ogundeji PS. Vitamin D, bilirubin and urinary albumin-creatinine ratio in adults with sickle cell anaemia. *Arch Basic Appl Med.* 2014;2:77-82.
20. Shams T, Al Wadani H, El-Masry R, Zakaria O. Effect of prophylactic vitamin D on anesthetic outcome in children with sickle cell disease. *J Anaesthesiol, Clini Pharmacol.* 2014;30(1):20.

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