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Association of vitamin D deficiency and bone mass with liver and heart iron overload in transfusion dependent thalassemia

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ABSTRACT

Background: Transfusion dependent thalassemia patients are reported to have Vitamin D insufficiency/deficiency in many countries. Vitamin D hydroxylation occurs in the liver; whether liver iron overload interferes with this step has not been addressed till date. This study helps to establish an association between liver iron concentration (LIC) and heart iron concentration (MIC) with vitamin D levels and Bone Mass Density in these patients.

Methods: A cross sectional study was done by including transfusion dependent Thalassemia patients (TM) if they had an assessment of Liver and cardiac iron done by T2*MRI and bone mineral density by DEXA. Clinical data regarding age, gender, type of iron chelation therapy and laboratory data of S. ferritin and Vitamin D was collected. Data was assessed using appropriate statistical methods.

Results: Among 40 TM patients were taken and mean age was 17.6 years. Vitamin D deficiency was identified in 26(65%). 20 out of them had an LIC>7mg/g DW and 6 had MIC>1.65mg/g DW. There was a significant association between LIC>7mg/g and vitamin D level<20 ng/ml and a significant inverse correlation between LIC and vitamin D, suggesting that liver iron overload may indeed affect vitamin D metabolism. Osteopenia was present in 32.5% and osteoporosis was present in 27.5 % of all TM patients. Reduced Bone Mass Density was also found to be linked with iron over load.

Conclusions: Regular monitoring of vitamin D levels and supplementation is required in patients with severe liver and heart iron load. More studies are needed to confirm these results.

Keywords: Chelation, Osteopenia, Vitamin D insufficiency

INTRODUCTION

Regular blood transfusion in thalassemia patients who are transfusion dependent leads to iron-overload that requires monitoring and management through long-term iron chelation therapy. Most common causes of death are cardiac arrhythmias, cardiomyopathy, and heart failure, while endocrine abnormalities contribute significantly to morbidity and mortality in these patients. ¹ Although survival of patients with thalassemia major has progressively improved with improvement of chelation

therapy; however, osteoporosis and cardiac dysfunction remain frequent complications. Adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk.

In thalassemia patients bone diseases like osteoporosis, rickets, scoliosis, spinal deformities, nerve compression and fractures are important cause of morbidity. $^{2-4}$ Impaired calcium homeostasis is a result of iron overload seen in β -thalassemic regular transfused patients. Both defective synthesis of vitamin D and hypoparathyroidism

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have been described in these patients and negatively affect their bone metabolism leading to complications. ⁴⁻⁸

In addition many factors can compromise the adaptation process to vitamin D deficiency which includes IGF-I deficiency, hypoparathyroidism due to iron deposition in parathyroid gland, delayed puberty hypogonadism, decreased bone mass and decreased synthesis of 25-OH-D, due to hepatic siderosis. 9,10,4 Various studies have demonstrated Vitamin D to be crucial for bony health in patients hemoglobinopathies. 11,12 Hence regular monitoring in this aspect and timely management is essential.

Hepatic osteodystrophy (HO) is a complex of structural and metabolic changes resulting in alterations in bone mineral metabolism in which vitamin D hydroxylation in the liver is affected. Studies suggest that there is a higher incidence of HO in cholestatic liver disease, and that serum 25-OH D3 continues to decrease as cirrhosis develops. ¹³ Chow et al, showed in patients with hereditary hemochromatosis that removal of excess iron by therapeutic venesection produced a significant increase in the mean serum 25-OH D3 level. ^{14,15}

As limited literature is available about the correlation between iron overload assessed by LIC and endocrinopathies as well as its correlation with Bone Mass Density in patients with TM, so this study was planned to examine a possible association between vitamin D levels and the severity of liver iron loading and to determine whether vitamin D hydroxylation may be affected by the presence of iron overload in the liver. ¹⁵

METHODS

Transfusion dependent Thalassemia patients were enrolled from Thalassemia Day Care centre at a Tertiary Care Teaching Hospital. Patients were enrolled from January 2019 to December 2019 who are coming for regular blood transfusion. Records of all the patients were checked and those patients were included who had an assessment of liver iron concentration (LIC) and heart iron concentration (MIC) done by MRI (T2*) and detailed endocrinal evaluation including DEXA scan as a part of routine work up in follow up visits.

Patients who did not give consent and not on regular follow up were excluded from the study. Ethical clearance was obtained from institutional ethical committee and informed consent from parents was obtained.

Demographic details in firm of age, sex, ethnicity was recorded. History of intake chelating agents, vitamin D, Calcium and frequency of blood transfusion was obtained from the subjects. Recent laboratory values of serum calcium, phosphate, liver function tests, kidney function tests were recorded from their case files.

Vitamin D (25 OH D3) levels were done in all those subjects included in the study. Patients were divided into groups with normal vitamin D with values ≥ 20 ng/ml, insufficiency with values < 20 and ≥ 12 ng/ml and deficiency with values < 12 ng/ml. LIC (Liver Iron Concentration) values which were taken were interpreted as LIC ≤ 2 mg/gm Dry Weight (DW) is normal; > 2 but ≤ 5 mg/gm DW is mild; > 5 but ≤ 7 mg/gm DW is moderate and > 7 mg/gm DW is considered as severe hepatic iron overload. MIC (Myocardial Iron Concentration) values were interpreted as values > 1.65 mg/g DW is taken as severe iron overload.

BMD was determined by DEXA scan. Osteopenia was defined as a Z score < -1.5 while < -2.5 indicated osteoporosis. Association between LIC (> 7mg/g) and MIC (> 1.65 mg/g) with vitamin D level and BMD in DEXA levels was examined.

Statistical analysis was performed using SPSS for Windows. Association between variables was determined by Chi-square or Fisher's Exact analyses, where appropriate. A two-sided P value of <0.05 was considered statistically significant. Pearson correlation coefficient was performed using SPSS.

RESULTS

Total 40 patients were enrolled out of 540 patients registered in Thalassemia Day Care centre in this Tertiary Care Teaching Hospital. M:F ratio was 3: 2 and mean age of subjects was 17.6 years. All patients were being transfused 3-4 weekly depending on their requirement to maintain pre transfusion Hb of \geq 9. All patients except one had received calcium supplementation and 37 had received vitamin D supplementation within last 1 year.

Out of which 21 had received weekly supplementation by taking vitamin D sachets and rest i.e. 16 have taken daily supplementation at a dose of 400-600 IU as a component of calcium containing syrups. Mean ferritin value was 2130 ng/ml. 18 patients had ferritin value between 1000-2000 ng/ml, 11 had value between 2000-3000 ng/ml and 4 had value between 3000-4000 ng/ml and 5 had value above 4000 ng/ml. Out of 40 patients, 26 were on deferasirox chelating agent, 4 on deferiprone, 7 were taking combination of both and 3 were taking injection deferoxamine in addition to deferasirox.

Serum calcium, phosphate were within normal limits in maximum no of patients (95%). Serum levels of vitamin D was suppressed in this thalassemic patients. Vitamin D deficiency was identified in 26(65%). 20 out of them had an LIC > 7mg/g and 6 had MIC > 1.65mg/g. But there were 4 patients with LIC>7mg/g and 1 patient with MIC > 1.65 mg/g whose Vitamin D levels were normal. 13(32.5%) and 11 (27.5%) patients were reported to have osteopenia and osteoporosis respectively among all TM patients (Table 1).

Table 1: Various characteristics of transfusion dependent thalassemia patients.

Characteristics	N (%)		
Ago	10-20 years		
Age	(mean = 17.6 years)		
Sex			
Male	24 (67%)		
Female	16 (33%)		
Type of chelation therapy			
Deferasirox	26 (65%)		
Deferiprone	4 (10%)		
Deferasirox + deferiprone	7 (17.5%)		
Desferroxamine + deferasirox	3 (7.5%)		
Vitamin D supplementation			
Taken	37 (92%)		
Not taken	3 (3%)		
Ferritin values			
< 1000 mg/ml	2 (5%)		
1001-2000 ng/ml	18 (45%)		
2001-3000 ng/ml	11 (27.5%)		
3001-4000 ng/ml	4 (10%)		
>4000 ng/ml	5 (12.5%)		
Vitamin D levels			
≥ 20 ng/ml	14 (35%)		
\geq 12 and \leq 20 ng/ml	16 (40%)		
<12 ng/ml	10 (25%)		
LIC (mg/gm DW)			
≤2 mg/gm	6 (15%)		
>2 and ≤ 5 mg/gm	6 (15%)		
>5 and ≤ 7 mg/gm	4 (10%)		
>7 mg/gm	24 (60%)		
MIC (mg/gm DW)			
≤1.65 mg/gm DW	2 3 (82.5%)		
>1.65 mg/gm	7 (17.5%)		
BMD			
Normal	16 (40%)		
Osteopenia (z score < -1.5)	13 (32.5%)		
Osteoporosis (z score < -2.5)	11 (27.5%)		

A significant association was noticed between 25-OH D3 level < 20 ng/ml and LIC > 7mg/g DW (p = 0.027). Moreover, there was an inverse correlation between LIC and 25-OH D3 level (correlation coefficient R= - 0.33). However, although out of 7 patients who had severe iron deposition in heart, 6 (85.7%) were vitamin D insufficient/deficient but correlation did not come out to be statistically significant (p= 0.206). No significant correlation was observed between vitamin D levels and ferritin values (p = 0.06) (Table 2).

DEXA scan showed mean Z score of -1.9 ± 0.19 and mean T score of -2.5 ± 0.24 . A significant correlation was also present in patients with severe liver iron concentration and osteopenia and osteoporosis (p=0.001). This correlation was not significant in case of heart iron

concentration as patients with MIC > 1.65 mg/g were very few. Along with that there was correlation between vitamin D insufficiency and reduced bone mass density in this study (Table 3).

DISCUSSION

Transfusion dependent thalassemia patients are known to be at risk of endocrinopathies and bone disorders. Vitamin D deficiency has been noted in both transfusion and non-transfusion dependent thalassemic patients and the mechanism is still not clear. 16,17

This study is a retrospective cross-sectional record-based study which addresses the prevalence of vitamin D insufficiency/deficiency in patients with transfusion dependent hemoglobinopathies in a single center along with its association with severe iron overload. Vitamin D deficiency/insufficiency was prevalent in our patient population despite supplementation in the majority (90%), which is in concordance of previous analyses.¹⁸

This study showed significant inverse correlation between iron deposition in liver and Vitamin D levels despite maximum number of patients were already supplemented with vitamin D supplements. This can be because of defective hydroxylation occurring in liver. These results were in concordance with a study in Columbia which has also shown association between vitamin D deficiency and elevated LIC, with an inverse correlation between the two parameters. ¹⁹

They found a significant association between liver iron overload (LIC >5mg/g DW) and moderate vitamin D insufficiency/deficiency (<60 nmol/L), suggesting that liver iron overload may affect vitamin D metabolism and possibly increase the risk of consequences related to vitamin D insufficiency/deficiency in them. This study has also concluded that liver iron overload may interfere with the first step in vitamin D metabolism, hydroxylation that occurs in the liver leading to its deficiency.

Although various studies have shown correlation of ferritin with LIC but serum ferritin may underestimate LIC in Non transfusion dependent Thalassemia or Thalassemia Intermedia.

In this study authors could not find any correlation between vitamin D levels and ferritin levels which may be because of factors affecting ferritin levels and small sample size. This result may also indicate that ferritin level is not an ideal marker of hepatic /cardiac iron overload and intensification of chelation targeting a normal LIC may be more important that decreasing ferritin levels.

This also presupposes that liver iron overload affects the first step of vitamin D hydroxylation in the liver and that offloading liver iron will improve this process.

Table 2: Association between LIC and MIC with vitamin D level <20 ng/ml.

	Vit D (<20 ng/ml)	Vit D (>20 ng/ml)	Total	p value	Odds ratio
LIC (> 7mg/g)	20	4	24 (60%)	0.027	8
LIC (<7 mg/g)	6	10	16 (40%)		
MIC (> 1.65mg/g)	6	1	7 (17.5%)	0.206	3
MIC (<1.65 mg/g)	20	13	33 (82.5%)		
Total	26 (65%)	14 (35%)	40 (100%)		

Table 3: Association between LIC and MIC with bone mass density.

	Normal BMD	Osteopenia	Osteoporosis	Total	p value
LIC (>7mg/g)	3	11	10	24 (60%)	0.001
LIC (<7mg/g)	13	2	1	16 (40%)	
MIC (>1.65mg/g)	-	4	3	7 (17.5%)	3
MIC (<1.65mg/g)	16	9	8	33 (82.5%)	
Total	16 (40%)	13 (32.5%)	11 (27.5%)	40 (100%)	

Vitamin D levels may prove to be better indicator of increased iron concentration in liver requiring urgent intervention specially in resource poor settings. Chelation therapy should be monitored not only by ferritin levels but also by T2*MRI as measurement of LIC and MIC is more sensitive indicators to determine complications in form of Vitamin D deficiency and reduced bone mass density. Intensification of chelation therapy is required to prevent vitamin D deficiency and consequences of decreased bone mass density.

An abnormality in calcium-parathyroid-vitamin D metabolism plays a role in the reduction in BMD. Serum levels of vitamin D which were suppressed in this thalassemic patients seems to be the one of the etiology behind decreased BMD in large number of patients. Abnormalities in sex hormone production or delayed puberty has also been proposed as a major precipitating cause of the reduction in BMD in thalassemic patients.²⁰ The hypothesis was confirmed by the improvement in BMD after hormone replacement in this group of patients.²⁰ Similar results were obtained in patients with hemochromatosis in whom BMD was decreased too and it was also attributed to defective 25-hydroxylation of vitamin D in the liver. 21,22 Athough this findings did not match study by Somnuek et al, and Rioja et al, who showed there was no correlation between bone disease and serum levels of vitamin D in patients, the remarkable elevation of serum ferritin level and prominent iron staining in trabecular bone indicated heavy iron overload to the body, and maybe, to the liver is noticed in all of the studies which favours iron overload as cause of vitamin D deficiency.^{23,24} However, this study shows positive correlation between vitamin D and BMD assuming defective hydroxylation can be a cause of both.

Major limitation of this study was its small sample size and absence of controls from non-transfused population. Such type of retrospective analysis and their results should be considered as hypothesis for future prospective analyses involving large number of patients.

CONCLUSION

Hence, authors recommend regular monitoring with timely supplementation of vitamin D levels in transfusion dependent thalassemia patients. Intensification of iron chelation therapy is also required to reduce the incidence of clinical consequences of vitamin D deficiency. Also, Vitamin D levels can be considered as surrogate marker of iron overload in liver which can be proven on further prospective studies.

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