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Assessment of Serum Vitamin D in Transfusion-Dependent B-Thalassemia Patients: Single-Center Observational Study

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Abstract

Background: Earlier surveys found that thalassemic patients on repeated blood transfusions unveiled substantial falls in vitamin D concentrations. This observational study aimed to assess vitamin D status among transfusion-dependent β-thalassemia major patients in Babylon City.Materials and methods: This is a single-center observational study comprising 304 patients with β-thalassemia major (184 males and 120 females) aged between 2.3-17.9 years. The next records were taken from all candidates: demographic features, age at first diagnosis, socioeconomic state, family history, residency, frequency of blood transfusions per month, types of chelating therapy; and laboratory examinations of serum vitamin D and ferritin. The statistical inspection had finished using the SPSS software version23. The qualitative parameters had stated as count +/- percentage, whereas the quantitative parameters had expressed as means +/- SD. A P-value of less than or equal to 5% reflected a significant value.Results: The mean ages of the patients were 12.8 ± 9.9 years, with the predominant male sex (60.5%), and around 2/3rd of them lived in rural areas and (62.1%) have a positive family history of thalassemia among the siblings. The main finding was a high frequency of hypovitaminosis D among thalassemia subjects (40.4%). As well, there was a nonsignificant association between the serum vitamin D levels and ferritin (*P*-0.3, *r*-0.11), a highly-significant negative association between vitamin D levels and the ages (*P*-0.3, *r* –0.3), and a highly-significant positive association between levels of ferritin and the ages (*P*-0.006, *r*-0.2) among the thalassemia patients.Conclusions: Our results suggest a high incidence of hypovitaminosis D among thalassemia subjects with a non-significant correlation between serum vitamin D levels and ferritin. As well, there was a highly significant correlation between ferritin levels and age among the thalassemia patients.

Keywords
Thalassemia, Iron overload, Ferritin, Vitamin D.

Introduction

Thalassemia syndrome is the most common anemia globally that involve a diverse group of anemia genotypes caused by defective hemoglobin synthesis, with rapid erythrocytes hemolysis (Al-hindy, Mousa, & Shaker, 2020; Hamayun, 2017) Thalassemia arises in around 28 x10^7 individuals that had led to 16,800 mortality in 2015 (H. A.-A. M. Al-Hindy et al., 2020; Dleikh et al., 2020). Clinically, thalassemic patients usually presented during early childhood complaining of asymptomatic or mild anemia extending to severe overt disease obligating permanent blood transfusions for survival (H. A.-a. Al-hindy et al., 2020). Frequent transfusions can cause iron overload in the blood with consequent multi-organ sequels including endocrine, hepatic, neurological, and metabolic systems (H. A.-a. Al-hindy et al., 2020; H. A.-A. M. Al-Hindy et al., 2020; Dleikh et al., 2020).

In contemporary eras, optimized transfusion regimes besides iron chelators have significantly enhanced the life prospects and outcomes of thalassemic children (H. A.-a. Al-hindy et al., 2020; H. A.-A. M. Al-Hindy et al., 2020; Saad et al., 2021). Conversely, high dosages of chelation therapy, like desferrioxamine (DFO), may aggravate bone complications like osteopenia and osteoporosis (Toumba & Skordis, 2010; Yu et al., 2019). Preceding studies of thalassemia patients have defined declines in calcium and vitamin D concentrations and subsequent defects in bone intensity and metabolism (Lertsuwan et al., 2018).

In this sense, earlier surveys found that thalassemic patients on a regimen of blood transfusions unveiled substantial falls in vitamin D concentrations of about 10-90% (Fung et al., 2011). This observational study aimed to assess vitamin D status among transfusion-dependent β-thalassemia patients in Babylon City.

Material and Methods

This was a single-center observational study comprising 304 patients with β-thalassemia major (184 males and 120 females) aged between 2.3-17.9 years. Patients had recruited from those recorded and followed up at ''Babylon Hereditary Blood Disorders Center in Babylon'' throughout the period from October 2020 to August 2021. The identification of β-thalassemia major cases was concluded by the pediatricians at the center. Thalassemic patients who were completely non-compliant to the regular blood transfusion, on vitamin D supplements, or severely disabled, and those with advanced renal impairment were excluded from the study. A research questionnaire had applied by the interrogator to record patients' characteristics during their admittance for regular RBCs regimen or follow-up appointments.

The next records were taken from all participants: demographic features; age at first diagnosis, socioeconomic status, family history, residency, frequency of blood transfusions per month, types of chelating therapy; and laboratory examinations of serum biochemistry.

Venous blood sampling vitamin D and ferritin analysis had collected from participants by vacutainer tubes. Vitamin D had analyzed by ELISA technique using 25(OH) vitamin D Calbiotech Inc. (Netherland). Ferritin levels had assessed by the "immunoturbidometric method (Spectrum®, Egypt)".

Ethical approval was acquired from the local hospital ethical committee. A written agreement was gained from the close relative of the encompassed patients.

The statistical inspection had finished using the SPSS software version23. The qualitative parameters had stated as count +/- percentage, whereas the quantitative parameters had expressed as means +/- SD. A P-value of less than 5% reflected a significant value.

Results

The baseline demographic characteristics of the studied subjects were presented in table-1. The mean ages of the patients were 12.8 ± 9.9 years, with predominant male sex of 184 (60.5%), around two-thirds of them lived in rural areas, and (62.1%) have a positive family history of thalassemia among their siblings. Of the total patients, 40% received a blood transfusion once monthly, and 47% twice monthly. 63.4% of cases were on oral Deferasirox (Exjade®) chelant therapy and 34% on classical DFO (Desferal®). The mean serum concentrations of vitamin D were 22.2 ± 13.8 ng/ml. Mean serum ferritin levels were relatively high among the patients 2978.9 ± 2081.3µg/ml, and most of them were underweight with a mean BMI reaching 20.8 ± 5.7kg/^{2}. About 1/4th of the patients have a good socioeconomic status, while 2/3rd of them had to some extent enough status.

Table-1: Main demographic characteristics of the thalassemia patients (N =304)

Variables		Descriptive statistics		
Age/years		Min 2.3	Max 17.9	Mean±SD 12.8 ± 9.9
Gender N (%)	Male	184 (60.5%)		
	Female	120 (39.5%)		
Age of thalassemia diagnosis/year N (%)	< 3 years	83 (27.3)		
	⩾ 3 years	221 (72.7)		
Frequency of transfusion/month N (%)	Once	143 (47)		
	Twice	122 (40)		
	Exceeding two times	39 (13)		
Residence N (%)	Rural	188 (61.9)		
	Urban	116 (38.1)		
Positive family history		190 (62.1)		
Socioeconomic state N (%)		Enough 75 (24.5)	Enough to some extent 192 (62.7)	Not enough 39 (12.7)
Chelating agents N (%)		Desferrioxamine 104 (34)	Deferiprone 194 (63.4)	No chelation 8 (2.6)
Vitamin D (ng/ml)		Min 2.0	Max 91.4	Mean±SD 22.2 ± 13.8
Ferritin (µg/ml)		Min 110	Max 12000	Mean±SD 2978.9 ± 2081.3
BMI (kg/m^2)		Min 9	Max 41	Mean±SD 20.8 ± 5.7

There was a high frequency (40.4%) of hypovitaminosis D among thalassemic patients. 59.6% of the thalassemic patients had sufficient vitamin levels in their sera, 30.3% had insufficient levels, and only 10.1% revealed vitamin D deficiency (figure-1).

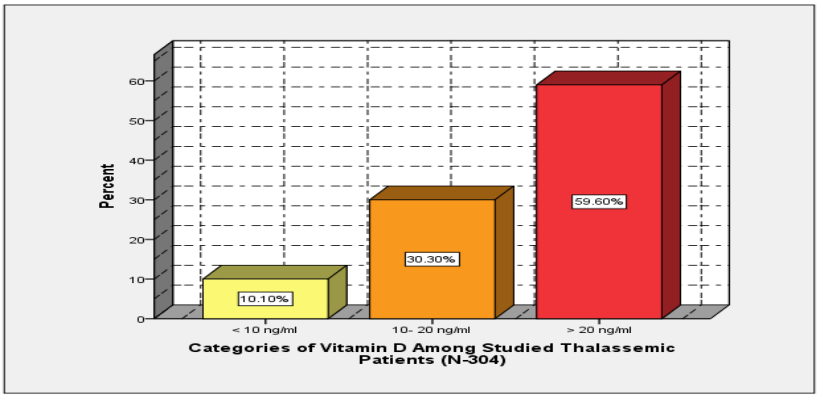

Figure-1: Distribution of thalassemia subjects according to the categories of vitamin D

The gender revealed no impact on the study variables other than vitamin D, which was significantly higher among the male patients (*P*-0.006) as shown in table-2. Likewise, the study variables were not influenced significantly (P> 0.05), when distributed according to the three vitamin D categories (table-3).

Table-2: Gender differences in the study variables among the study thalassemic patients

	Gender	Mean	P-Value
Age/year	M	16.2 ± 9.3	> 0.005
	F	15.7 ± 10.7	
Vitamin D (ng/ml)	M	28.1 ±18.1	0.006
	F	20.2 ± 10.3	
Ferritin (ng/ml)	M	3209.1 ± 2254.8	> 0.016
	F	2625.3 ±1747.4	
BMI (kg/m^2)	M	19.6 ±5.1	> 0.05
	F	21.9 ±6.1	

There were significant variations in mean values of serum vitamin D according to the residence of patients, frequency of blood transfusion, age at diagnosis, socioeconomic status, and types of iron chelators (results are not included).

Table-3: Distribution of the study variables according to the categories of the mean serum vitamin D levels among thalassemic patients

	Vitamin D Categories	Mean	Std. Deviation	P-Value
Ferritin (ng/ml)	Deficient	3407.2	2278.7	> 0.05
	Insufficient	2857.5	2013.8	
	Sufficient	3449.0	2253.0	
Age (year)	Deficient	18.1	8.9	> 0.05
	Insufficient	16.1	9.1	
	Sufficient	15.8	8.3	
BMI (kg/m^2)	Deficient	19.0	2.7	> 0.05
	Insufficient	17.9	3.2	
	Sufficient	18.0	2.8	

The correlation between the serum vitamin D and ferritin means was non-significant (*P*-0.3, *r*-0.11). A highly-significant negative correlation between the ages and vitamin D concentrations (*P*-0.3, *r* –0.3), and a highly significant positive correlation between levels of ferritin and ages (*P*-0.006, *r*-0.2) among the thalassemia patients (table-4).

Table-4: Correlation of ages and levels of serum ferritin with vitamin D among thalassemia patients

		Vitamin D	Ferritin	Age
Vitamin D	Pearson Correlation (*r*)	-	0.11	- 0.3
	Significance (*P*)	-	0.3	0.003
Ferritin	Pearson Correlation (*r*)	0.11	-	0.2
	Significance (*P*)	0.3	-	0.006
Age	Pearson Correlation (*r*)	- 0.3	0.2	-
	Significance (*P*)	0.003	0.006	-

Discussion

The question under discussion in this

observational study was vitamin D serum status among patients with transfusion-dependent β-thalassemia major in Babylon City. The main finding of the current study was a high frequency of hypovitaminosis D among thalassemia patients (40.4%). As well, the study revealed a non-significant correlation between the serum vitamin D and ferritin (*P*-0.3, *r*-0.11), a highly significant negative correlation between the ages and levels of vitamin D (*P*-0.3, *r* –0.3), and a highly significant positive correlation between levels of ferritin and the ages (*P*-0.006, *r*-0.2) among the thalassemia patients.

Several works can be advanced to support the outcomes of this study. A recent Chinese study involving 32 thalassemic patients, revealed significantly corresponding results (Yu et al., 2019). Another recent Iranian study conducted on 40 patients from Arak, Iran, exposed vitamin D3 levels in 82.5% of patients were less than 20 ng/dl, but not correlated with age (Shaykhbaygloo et al., 2020). Vitamin D concentrations were also fluctuating from 10-24 ng/ml in 39.1% of the total 69 thalassemic Saudi cases recruited in a retrospective cohort study three years ago (Tharwat et al., 2019). A previous Iraqi study revealed significantly lower vitamin D in thalassemia patients compared to the controls (Almosawi & Al-Rashedi, 2009).

Last decades, improved practices of packed cell transfusions and iron chelators have greatly enhanced the life expectations and life quality of thalassemia patients (H. A.-a. Al-hindy et al., 2020; H. A.-A. M. Al-Hindy et al., 2020; Dleikh et al., 2020). Nevertheless, advanced use of chelating agents, (e. g. DFO), might exacerbate thalassemic complications like bone resorption (Kuo & Mrkobrada, 2014). The earlier reports of thalassemia have detected reductions in serum levels of calcium and vitamin D with subsequent declines in bone density and metabolism (Gaudio et al., 2019). Nonetheless, the association between calcium and vitamin D with the risk of bony disorders in thalassemia syndrome remains unclear.

The available evidence seems to suggest that thalassemic patients on regular transfusion schedules revealed reduced vitamin D levels of approximately 10-90% (Almosawi & Al-Rashedi, 2009; Tharwat et al., 2019; Yu et al., 2019). In these cases, the enhanced intestinal iron absorption reduces calcium absorption significantly (Fung et al., 2011) Thus far, hypocalcemia has multifactorial etiology, which may include iron overload, reduced vitamin D and/or calcium absorption or ingestion, and hypoparathyroidism (Arabi et al., 2006; Masser et al., 2021). Another likely mechanism for reduced vitamin D is an inadequate liver function, such as hepatic toxicity of chelation therapy, and viral hepatitis infection (Napoli et al., 2006). Furthermore, vitamin D deficiency may be worsened by impaired outdoor events caused by anemia and skeletal complications (Piga, 2017).

The data gathered in the present study suggests the severity of vitamin D insufficiency is significantly correlated with age. This relationship remains uncertain, still, preceding scholars proposed an association with more indoor lifestyles or reduced vitamin D consumption in adolescent patients (Wood et al., 2008), or due to malabsorption as well (Fahim et al., 2013). Additionally, hepatic 25-hydroxylation of vitamin D might be impaired by hemosiderosis caused by iron overload (Chow et al., 1985). As well, decreased vitamin D production by the skin consequent to jaundice is an additional potential mechanism (Darvishi-Khezri et al., 2020). The latter two mechanisms might explain lower vitamin D concentrations in thalassemic patients in general and also explain lower vitamin levels among older children. Even though vitamin D and/or calcium supplementing are acclaimed to avoid osteoporosis, the ideal time for this approach has not been considered.

The correlation between plasma vitamin D and ferritin was non-significant in the existing study and was supported by other academics. A

report published in Indonesia revealed a non-significant correlation between serum vitamin D and parathyroid levels with that ferritin (Izzah, Rofinda, & Arbi, 2017). A Turkish study published in 2013 revealed no correlation between vitamin D and serum ferritin concentrations (Albayrak & Albayrak, 2013). Comparable results were also described by current Iranian researchers (Shaykhbaygloo et al., 2020). Meanwhile, among normal Canadians, those with serum higher vitamin D levels compared with those who had lower levels, were markedly less at risk for raised ferritin levels (Munasinghe et al., 2019).

On logical grounds, there is no compelling reason to argue that in thalassemia syndrome, vitamin D deficiency is not merely a concomitant finding, but as well an exaggerating factor for the primary complications of thalassemia.

Conclusions

Our results suggest that hypovitaminosis D was prevalent among thalassemia subjects with a non-significant correlation between vitamin D and serum ferritin. As well, a highly significant positive correlation between the concentrations of ferritin and age among thalassemia patients. Our conclusions may afford an important medical indication of the necessity for intervention to avoid undue complications in thalassemia major patients.

Limitations

This study had some notable limitations, like a single-center design, which may have prohibited our capacity to get significant generalized outcomes, all over Iraqi patients. We did not study the impacts of some variables that may affect vitamin D measures like physical activity and the dietary state. Lastly, we did not compare the findings with healthy children. Even supposing the outcomes of this study assume otherwise, owing to the limitations, we cannot disregard the probability that insufficient vitamin D was an epiphenomenon instead of a contributory modulator of iron loading. However, the current outcomes are satisfactorily convincing to initiate larger cohort studies to confirm the current outcomes.

Conflict of interest

we confirmed that there were no conflicts of interest.

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