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Original Article

Prevalence of Endocrine Complications in Transfusion-Dependent Beta Thalassemic Pakistani Patients

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Abstract

Objectives: To investigate the frequency of endocrine complications among β-thalassemic patients in Pakistan.
Materials and Methods: The current cross sectional study was conducted at the Thalassemia Centre, Islamabad, Pakistan between October 2013 and March 2014. We enrolled 96 β-thalassemic patients and blood samples were drawn to determine serum calcium, phosphate, ferritin, parathyroid hormone, free T4, thyroid stimulating hormone, 25-hydroxy vitamin D and random blood sugar levels. Comparison of demographic features and serum ferritin levels between patients with endocrine and without endocrine complication was done using logistic regression analysis and odds ratio (OR), 95% confidence interval (CI) and p-values were reported. The level of significant was considered at 5%.
Results: Out of 96, 56 (58.3%) were male patients. The mean (±SD) age and ferritin levels of patients was 13.8 (±3.8) years and 4447 (±2945) ng/mL, respectively. Out of 96, 40 (41.7%) patients had endocrine complications – hypoparathyroidism (24.0%), hypothyroidism (13.5%), vitamin D deficiency (3.1%) and diabetes (1.1%). Thalassemic patients who had higher serum ferritin levels (3000 ng/ml or more) had significantly higher odds of endocrine complications (OR 5.42, p=0.038) compared to those who had low serum ferritin levels (<1500 ng/ml) adjusted for age and gender.
Conclusions: Slightly over two-fifths of β-thalassemic patients had endocrine complication. A quarter of patients had hypoparathyroidism, while one in seven patients had hypothyroidism. A strong association between the endocrine complications and a high serum ferritin level was found in our study population. Hypogonadism is picked at pubertal age group, and Diabetes occurs in second decade and our selected group was mostly prepubertal.
Key words: β-thalassemia, endocrine complications, hypoparathyroidism, hypothyroidism, serum ferritin.

Introduction

Globally, β-thalassemia is considered as the most common autosomal recessive disorders. The condition is caused by the reduced or absent synthesis of the β globin chains of the haemoglobin tetramer, which is made up of two α globin and two β globin chains.[1] It is manifested by anaemia, hepatosplenomegaly, growth retardation, bone changes. A high prevalence of thalassemic patients has been reported from Mediterranean, Middle-East, Central Asia, Indian subcontinent, and Far East.[1] In Pakistan, the gene frequency of β-thalassemia is estimated to be ranged from 5% to 8%[2] and it is present in all ethnic groups.[3] It is estimated that there are approximately 9 million carriers of β-thalassemia, resulting in more than 5000 transfusion-dependent births every year in Pakistan.[4]

Repeated blood transfusions, with irregular and poor chelation therapy, led to iron overload, which resulted in frequent endocrine complications. The standard management of severe β-thalassemia is a combination of regular blood transfusion with an attempt to maintain haemoglobin levels between 9g/dl to 10 g/dL and iron chelation therapy.[5] As a results of the combination of regular blood transfusion and chelation, complications can be prevented and the life span

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of these patients has been extended.[6] Improper chelation therapy, repeated blood transfusions leads to iron overload, which results in frequent endocrine complications such as hypothyroidism and hypoparathyroidism[7], hypogonadism, diabetes mellitus.

Hypoparathyroidism has been considered as a typical complication of the second decade of life in transfusion-dependent patients with β-thalassemia.[8, 9] The prevalence of hypoparathyroidism in β-thalassemic patients in various study populations ranges from 2.5% to 40%.[7, 8, 10-13] Hypoparathyroidism can lead to hypocalcemia and severe osteoporosis.[8, 14] Hypoparathyroidism may cause various manifestations also, including tetany, seizures, carpopedal spasms, and paresthesia.[15] The most plausible mechanism is related to iron overload and its associated tissue damage, in addition to, oxidative stress, lipid peroxidation and free radicles release.[16] Hypothyroidism is also a common endocrine complication in β-thalassemic patients.[17] However, its prevalence and severity varies in different populations and its long-term natural history is yet to be clear.[2] Earlier studies have reported a prevalence of hypothyroidism ranging from 0 to 35% in β-thalassemic patients who were on regular blood transfusions.[18, 19] However, the prevalence of hypothyroidism in β-thalassemic patients depends on the age of the study population, duration of blood transfusions, ferritin levels and dose and compliance of the iron-chelating agent.[18, 19]

The study aimed to determine the prevalence of endocrine complications in β-thalassemic patients in Pakistan. Moreover, we investigated the frequency of each of the endocrine complication in our study population. In addition, we also examined the association of endocrine complications with demographic features and serum ferritin levels.

Materials and Methods

The study aimed to determine the prevalence of endocrine complications and to investigate the association between endocrine complications and serum ferritin levels in β-thalassemic patients in our clinical settings.

Study design, population and site: The current cross sectional study was conducted at the Thalassemia Centre, Pakistan Institute of Medical Sciences, Islamabad, Pakistan. The Thalassemia Centre was established in 2005. The Thalassemia Centre caters thalassemic patients from various regions of the country. In the current study, we enrolled β-thalassemic patients who were presented to the Thalassemia Center for management between October 2013 and March 2014. Most patients, were on irregular blood transfusion regimen, but again a poor compliance to our chelation protocol either due to financial or their family issues. Decided chelation protocol was desferrioxamine 40-60 mg/kg 5 days per week and deferiprone 75 mg/kg/day.

Patients with β-thalassemia intermedia, with acute illness, with a family history of hypothyroidism or who were already diagnosed to have any endocrine complications were not included in the study. Informed consent was obtained from patients or their parents/caregivers in case of children. Before the commencement of the study, ethics approval was obtained from the Hospital Ethics Committee, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.

Data collection procedure: At the time of enrolment, information regarding the demographic features and clinical examinations were collected from each patient. Blood samples were drawn from each of the enrolled patient at the time of enrolment to determine serum calcium (normal range 2.1-2.5 mmol/l), phosphate (normal range 0.8-1.5 mmol/l), ferritin (normal range male: 12- 300 ng/ml; female: 12-150 ng/ml), parathyroid hormone (PTH) (normal range 1.6-9.3 pmol/l), free T4 (normal range 0.8-2.0 ng/dl), thyroid stimulating hormone (TSH) (normal range 0.3-4.0μIU/ml), vitamin D-3 (25-hydroxy vitamin D) and random blood sugar levels. Thyroid function was evaluated by measurements of T4, and TSH using enzyme-linked immunosorbent assay (ELISA). Hypothyroidism was defined by a TSH level >8μIU/ml, and T4 levels <4.5μg/dl. Iron load status was defined by serum ferritin level that was estimated from pre-transfusion blood sample. Parathyroid function was assessed by measurement of PTH using ELISA. Hypoparathyroidism was defined as low levels of PTH (<1.6 pmol/l) or normal levels of PTH in the presence of low serum calcium levels (<2.1 mmol/l). Serum vitamin D3 levels of ≥30 ng/mL were defined as normal, 20-30 ng/mL as insufficient, and <20 ng/mL as deficient. A random blood glucose level of ≥200 mg/dL was considered diabetes mellitus.

Sample size and statistical analysis: Using a standard formula for single proportion[20], and assuming 50% prevalence of any endocrine complication in β-thalassemic patients, absolute precision as 10%, and with 95% confidence level, the sample size for descriptive analysis was calculated to be 96 β-thalassemic patients.

Data was entered using Microsoft Excel while analysis was conducted using STATA 12.1 (Stata-Corp, College Station, TX, USA) software. Descriptive analysis was performed to calculate the frequencies and percentages for categorical variables and mean (±Standard deviation) with median (interquartile range) for continuous variables. For comparison

between the patients who had any endocrine complication with those who did not have any endocrine complication, we performed a multivariable logistic regression analyses. Logistic regression analysis calculated odds ratio (OR), 95% confidence interval (CI) and p-value. A p-value less than 0.05 was considered as significant.

Results

A total of 96 β-thalassemic patients were enrolled in the current study. Table 1 presents the demographic features and laboratory findings of all the enrolled patients. Out of 96, 56 (58.3%) were male patients. The male to female ratio was 1:1.4. The mean (±SD) age of patients was 12 (±1.3) years with an interquartile range between 11 and 15 years. Majority of patients [n=81 (84.4%)] were between 11 and 15 years of age. The mean (±SD) ferritin levels at the time of enrolment was 4447 (±2945) ng/ml. Forty-two (43.7%) patients had serum ferritin level, 3000 ng/ml or more. The mean (±SD) serum phosphorus and calcium levels were 5.4 (±1.7) mg/dl and 1.6 (±1.8) mg/dl, respectively.

Table 1. Demographic features and laboratory findings of β-thalassemic patients (n=96)

Variables	n	%
Demographic features		
Gender		
Male	56	48
Female	40	42
Age (in years)		
Mean (SD)	12.3	(±1.5)
Median (IQR)	13	(11.5-16.0)
Age categories		
Up to 10 years	15	15.6
11 to 15 years	81	84.4
Laboratory findings		
Serum ferritin		
Mean (SD)	4447	(±2945)
Median (IQR)	3580	(2380-5668)
Serum ferritin level categories		
Less than 5000	61	63.5
5000 and more	35	36.5
Serum phosphorus		
Mean (SD)	5.4	(±1.7)
Median (IQR)	5.0	(4.0-6.5)
Serum calcium		
Mean (SD)	1.6	(±1.8)
Median (IQR)	1.1	(1.1-1.3)
Serum TSH		
Mean (SD)	12.6	(±4.6)
Median (IQR)	13	(11.0-15.0)
Serum T4		
Mean (SD)	4.7	(±4.7)
Median (IQR)	3.2	(2.2-5.2)
Blood random sugar		
Mean (SD)	103.6	(±24.9)
Median (IQR)	98.0	(92.0-110.0)
Vitamin D3		
Mean (SD)	14.5	(±7.7)
Median (IQR)	11.5	(9.5-18.0)

IQR: Interquartile range.
SD: Standard deviation

Figure 1 shows the percentage distribution of β-thalassemic patients by the status of endocrine complications. Out of 96, 56 (58.3%) patients had no endocrine complication at the time of enrolment. The most common complication was hypoparathyroidism which was present in 23 (24.0%) of patients, followed by hypothyroidism [n=13 (13.5%)], vitamin D deficiency [n=3 (3.1%)] and diabetes mellitus [n=1 (1.1%)].

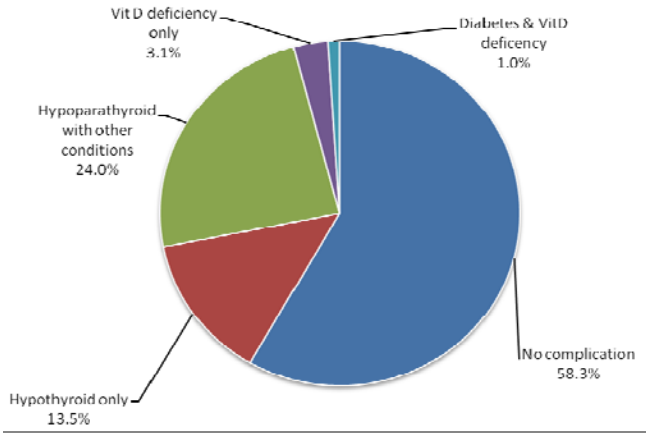

Figure 1: Percentage distribution of β-thalassemic patients by status of endocrine complications (n=96)

Out of 23 patients with hypoparathyroidism, 13 (56.5%) had hypoparathyroidism only, while 10 (43.5%) patients with hypoparathyroidism also had other complications such as hypothyroidism (n=6), vitamin D deficiency (n=3) and diabetes mellitus (n=1).

The comparison of demographic features and serum ferritin levels between the thalassemic patients with and without endocrine complications is presented in Table 2. No significant differences were seen in gender (p=0.889), and age (p=0.371) of patients between those who had endocrine complications and those who did not have complications. We found a significant association between a higher serum

Table 2. Comparison of demographic features and serum ferritin levels of β-thalassemic patients with and without endocrine complications: findings of multivariable logistic regression analysis (n=96)

	Endocrine complications (n=40)		No endocrine complications (n=56)				
Variables	**N**	**%**	**n**	**%**	**OR**	**(95% CI)**	**p-value**
Demographic features							
Gender							
Male	23	57.5	33	58.9	1.00		
Female	17	42.5	23	41.1	1.06	(0.47 - 2.41)	0.889
Age (in years)							
Mean (SD)	13.4	2.4	14.1	4.5			0.371
Median (IQR)	13.0	(12.0-16.0)	13.0	(11.0-15.0)			
Age categories							
Up to 10 years	4	10.0	11	19.6	1.00		
11 to 15 years	26	65.0	30	53.6	2.38	(0.68 - 8.37)	0.176
More than 15 years	10	25.0	15	26.8	1.83	(0.45 - 7.41)	0.395
Serum ferritin level categories							
<1500	2	5.0	12	21.4	1.00		
1500 - 2999	7	17.5	12	21.4	3.14	(0.52 – 19.00)	0.213
≥3000	31	77.5	32	57.1	5.11	(1.10 – 26.68)	0.038

IQR: Interquartile range. OR: Odds ratio. SD: Standard deviation.

ferritin levels and the presence of endocrine complications. With serum level of ferritin of 3000 ng/ml or more the odds of presence of any endocrine complication was 5 times higher (OR 5.42, 95% CI 1.10 – 26.68, p=0.038) than to serum level of less than 1500 ng/ml in thalassemic patients after adjusted for age and gender.

Discussion

Main findings and its significance: The current study was conducted to investigate the frequency of endocrine complications among β-thalassemic patients in Pakistan. We found that of 96 β-thalassemic patients enrolled in the current study, 40 (41.7%) had endocrine complications at the time of enrolment. The most common endocrine complication was hypoparathyroidism (24.0%), followed by hypothyroidism (13.5%). Although the diabetes and gonadal damage usually occur in late second decade of life in thalassemia patients, we have seen few patients in our study who had vitamin D deficiency (3.1%) and diabetes mellitus (1.1%). A strong association between the presence of endocrine complications and a higher level of serum ferritin (3000 ng/ml and more) was observed in our study population. Iron overload is the main contributor which damages almost every organ of the body. It has been reported that hypothalamus and/or pituitary can be damaged leading to multiple pituitary hormone deficiency. Heart is affected due to iron overload and leads to dilated cardiomyopathy, pulmonary hypertension can be seen later on. Liver is prone to be fibrotic or cirrhotic and damage of pancreas leads to diabetes which usually develops in late second decade of life. Gonadal damage also occurs which results in hypogonadism again noted at pubertal age and vitamin D deficiency consequences to osteoporosis. Toxicity to endocrine glands results in hypothyroidism, hypoparathyroidism or gonadal damage Skin discoloration also occurs as a consequence of iron deposition.[21] Our study findings are important for clinicians managing β-thalassemic patients in a similar clinical setting. Timely identification of poorly transfused B thalassemia patients, periodic measurement of serum ferritin level and further management of endocrine complications, if it occurs improves quality of life of these patients.

Comparison with other studies: In the current study we found a high prevalence of endocrine complications in our study population. The prevalence of hypoparathyroidism (24.0%) in β-thalassemic patients in our study was also higher compared to several studies from various countries like Oman (19%)[7], Iran (7.6% to 14.6%)[10, 11], Greece (13.5%)[12] and China (10.7%)[8]. Nevertheless, a retrospective study from Karachi, Pakistan found a higher prevalence of hypoparathyroidism (40%) among β-thalassemic patients[13] than what we have

found. The prevalence of hypothyroidism was 13.5% in our study, which was higher than from a previous study from Pakistan (11.8%)[13], and Iran.[11] However, a study from Greece reported a slightly higher prevalence of hypothyroidism (17.5%).[18] The plausible explanation of variation in prevalence of hypoparathyroidism and hypothyroidism in our study could be due to the fact that the β-thalassemic patients in our study were older and chelation therapy was also initiated later in their life in our study population. Few patients reported to have vitamin D deficiency (3.1%) and diabetes mellitus (1.1%) in our study population. Napoli et al found that 9.6% of thalassemic patients had vitamin D deficiency in their population in Italy.[22] Earlier Dandona and co-workers from UK assessed the levels of vitamin D in 15 thalassemic patients and found that thalassemic patients had significantly lower levels of vitamin D compared to controls.[23] A recent review reported that 6-10% of thalassemic patients had diabetes due to iron overload.[24] Chern and Lin found that only 7% of thalassemic patients had diabetes in their study population in Taiwan.[8] In Iran, Hamidieh et al found that 15.8% of thalassemic patients with hypoparathyroidism had diabetes mellitus also in their study population.[10] Zervas and colleagues found that 13% of thalassemic patients had diabetes in their study population.[18]

Biological Mechanism: Endocrine complications such as hypoparathyroidism and hypothyroidism are a well recognized complication of β-thalassemic patients due to chronic anaemia, and iron overload.[7] In agreement with other studies published previously[17, 19], our study findings showed a higher percentage (77.5%) of patients with endocrine complications had 3000 ng/ml or more serum ferritin levels compared to those who did not have any complications (57.1%). Further, our study also found a strong association between endocrine complications and a higher serum ferritin levels compared to lower levels. The standard management of severe β-thalassemia is a combination of regular blood transfusion with an attempt to maintain haemoglobin levels greater than 10 g/dL and iron chelation therapy.[5] It is reported that higher ferritin levels contribute to damage to various body organs. Thalassemia patients, who do not receive regular optimal transfusions, often have anaemia, which leads to extramedullary haematopoises such as liver, spleen, facial bones, lymph nodes, spine etc. Consequently, there is an enlargement of liver, spleen, and thalassemic facies, which is noted in all patients who receive poor transfusions. Extramedullary heamopoises is a sign of hypoxic effect secondary to poor transfusion which is also a contributory factor for organ damage. Thus, a high ferritin levels with anaemia in these patients causes organ damage and develops endocrine complications. On the other hand, patients who are receiving regular optimal transfusions are free of anaemic and hypoxic damage. However, regular transfusions without proper chelation prevent anemia and hypoxic damage but poor chelation results in overload of iron which leads ferritin toxicity and organ damage.[25]

Strength and limitations: The current study was conducted at the Thalassemic Centre at a tertiary care hospital which caters patients from a wide range of area. Hence, the study population of the current study represented a wide area of Pakistan, which was the main strength of the current study. Further, the sample size was adequate to allow us to determine the prevalence of overall as well as individual endocrine complication in β-thalassemic patients in our study. Further, we conducted logistic regression analysis to examine the association between higher levels of serum ferritin and presence of endocrine complication after adjusted for age and gender of patients.

One of the study limitations was the nature of the temporal relationship between exposures and outcomes as the data was collected in a cross-sectional study design and both were measured at the same time. Further, the data regarding the duration of blood transfusion and chelation therapy, which could affect the status of endocrine complications, were not collected in the current study. However, these limitations are important but are unlikely to have had an important effect on the validity of our findings.

Conclusion

In conclusions, we found slightly over two-fifths of β-thalassemic patients had endocrine complications. A quarter of β-thalassemic patients in our study had hypoparathyroidism while one in seven patients had hypothyroidism. A strong association between the presence of endocrine complications and high levels of serum ferritin was found in our study population. This shows that high serum ferritin levels contribute to the development of endocrine complications in patients who are not receiving optimal transfusions. There is

a need to conduct a multicentre, large sample size, cohort studies to determine the true prevalence of various endocrine complications in patients with β-thalassemia in Pakistan.

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