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Assessment of Subclinical Hypoparathyroidism and Hypocalcemia in Patients with Beta Thalassemia Major at Suez Canal University Hospital

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ABSTRACT

Background: Thalassemia, an inherited blood disorder, is a global health concern. B-thalassemia major leads to impaired erythropoiesis and increased hemolysis. Blood transfusions can cause iron overload and endocrine complications, including hypoparathyroidism. Understanding hypocalcaemia mechanisms is crucial for effective treatment and prevention.

Aim: This study aimed to evaluate subclinical hypoparathyroidism and hypocalcaemia among patients with transfusion-dependent beta thalassemia major for early diagnosis and management.

Patients and methods: Each participant's informed consent was obtained before using a structured interview-based questionnaire included individual sociodemographic details, comorbid chronic diseases make up the second section, the patient's current drugs, and the surgical procedures like splenectomy and thyroidectomy, and laboratory investigations.

Results: The study involved 73 thalassemic patients, with a mean age of 26.2 years, 54.5% females, and 35.5% males. Majority of hypocalcaemia cases were asymptomatic, and the prevalence of hypoparathyroidism was 24.7%. Patients with hypoparathyroidism had higher levels of PTH and total & ionized calcium, while ferritin concentration was higher. Advanced age, treatment compliance, and ferritin were significant risk factors.

Conclusion: Individuals with transfusion-dependent thalassaemia frequently experience hypoparathyroidism and hypocalcaemia, which may be brought on by inadequate chelation. In individuals with iron excess, hypocalcaemia is often asymptomatic and persistent.

Keywords: Iron overload, Endocrine complications.

INTRODUCTION

Thalassemia, an autosomal recessive inherited blood disorder, significantly impacts global health. Beta thalassemia major (β-thalassemia) is characterized by the impaired synthesis of beta globin chains, resulting in ineffective erythropoiesis and increased peripheral hemolysis. The chronic need for repeated blood transfusions in patients with β-thalassemia is essential for managing anemia and to sustain life. However, repeated transfusions frequently contribute to iron overload, and also precipitating a range of endocrine complications. Among these complications hypoparathyroidism (HPT), emerged as a notable concern, a condition that is associated with severe hypocalcaemia and its consequential neurological manifestations, including tetany, seizures, and carpopedal spasms [(1, 2)].

While overt hypoparathyroidism in β-thalassemia is relatively rare, existing literature suggests that subclinical or asymptomatic forms may be more prevalent than previously recognized [(3)]. **Gabriele [(4)]** was the first to describe HPT in thalassaemia patients due to siderosis. In fact, a study conducted by **Even *et al.* [(5)]** highlighted an alarming incidence rate of up to 42% of asymptomatic hypoparathyroidism [(5)].

Calcium, an essential trace metal and the most common cation in the human body, constitutes 1.5–2% of total body weight. The relationship between calcium homeostasis and parathyroid hormone (PTH) dysregulation is intricately linked to various physiological functions, including skeletal mineralization, excitability of skeletal and cardiac muscles, exocrine gland stimulation, and maintaining cell membrane integrity and permeability, particularly in relation to sodium and potassium exchange, nerve conduction, blood coagulation, vascular tone regulation, and many other physiological processes. Hypocalcaemia, defined by reduced calcium levels, arises through parathyroid hormone (PTH)-mediated or non-PTH-mediated mechanisms [(6)].

In thalassemia patients, iron-mediated damage to the parathyroid glands is a key factor, driven by increased collagen deposition by elevated activity of the iron-dependent protocollagen propyl hydroxylase enzyme, susceptibility to iron damage, and a patient's microcirculation being disrupted. These pathophysiological changes lead to impaired PTH

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production, decreased bone remodeling, reduced intestinal calcium absorption, and an increase in renal calcium excretion, culminating in hypocalcaemia [7, 8].

Understanding the mechanisms underlying hypocalcaemia in thalassemia patients is crucial for effective treatment and prevention strategies. Recognizing these complexities, our study aimed to thoroughly evaluate the prevalence of subclinical hypoparathyroidism and hypocalcaemia among patients with transfusion-dependent beta thalassemia major at Suez Canal University Hospital. By shedding light on the incidence and implications of these endocrine complications, we hope to enhance the understanding of their potential neurological manifestations, and to provide insights that can guide patient management and improvement of clinical care and outcomes for individuals living with β thalassemia major.

PATIENTS AND METHODS

An analytical cross-sectional study was conducted at **Hematology Inpatient Unit and Clinic, Internal Medicine Department, Suez Canal University Hospital, Ismailia, Egypt.**

73 participants TDT patients with iron overload aged >18 years were **recruited** from the Hematology inpatient ward, and outpatient clinic**.**

Exclusion criteria: Patients with other types of thalassemia, renal insufficiency (e-GFR < 30), bone marrow transplantation, regularly taking proton-pump inhibitors, and those with thyroidectomy.

The questionnaire included five sections:

Individual Sociodemographic details, such as age, sex, employment, place of residence, unique habits, marital status, etc., were included in the first section. Comorbid chronic diseases made the second section. The patient's current drugs made the third section. The fourth section covered surgical procedures like splenectomy and thyroidectomy. Laboratory investigations made the fifth section. Blood samples were collected for assessing CBC, parathyroid hormone, serum calcium and ferritin.

The interview-based questionnaire

1- Sociodemographic data:
Name:
Age:
Sex:
Occupation:
Residence:
Special habits:
Marital status:

2- Chronic illness:
Cardiac:
Hepatic:
Gastroenterology:
Pulmonary:
Hematology:
Cancer:
Autoimmune diseases:

3- Drugs:

Drug	Yes	No
Iron chelating agent		
Calcium supplement		
Proton pump inhibitor		

4- Surgical intervention:

Surgery	Yes	No
Bone marrow transplantation		

5- Biochemical markers:

chemistry Blood	Value	Deficient	Sufficient
Hemoglobin (g/dl)			
Ferritin (ng/ml)			
Total serum calcium (mg/dl)			
Ionized serum calcium(mg/dl)			
Serum PTH (pg/ml)			

Hypocalcaemia is defined as serum levels below the normal range of 8.5–10.5 mg/l for total calcium and 4.65–5.25 mg/dl for ionized calcium [13]. Normal PTH level is 15 – 65 pg/ml, levels below that are considered hypoparathyroidism [14].

Assessing and tracking iron homeostasis, which included measuring serum ferritin (SF), is one way to determine iron overload. When SF readings exceed 1000 ng/mL, iron overload is present [15].

Ethical approval: The Ethical Committee at the Faculty of Medicine, Suez Canal University, Egypt, approved this study. All patients gave their written informed consents before their enrollment in this study. The study complied with the Helsinki Declaration throughout its implementation.

Statistical Analysis

Version 20.0 of the IBM SPSS software suite was used to analyze the data. (IBM Corp., Armonk, NY). Interquartile ranges (IQR), medians, or percentages, and means ± standard deviation (SD) are used to represent descriptive statistics.

The normality of the distribution was confirmed using the Kolmogorov-Smirnov test. The frequency of qualitative characteristics across the various groups was compared using the Chi-square test. For quantitative variables that were regularly distributed, the student t-test (t) was employed to compare the two groups under study. The odds ratio (OR) with 95% CI was assessed using univariate logistic regression analysis. P-values ≤ 0.05 were regarded as statistically significant.

RESULTS

Table (1) showed that 73 thalassemic patients were recruited in this study, including 38 (54.5%) females and 35 (45.5%) males. The mean age of the patients was 26.2 ± 5.9 years, 38 (54.5%) were married, 35 (45.5%) were single, 63% were urban and 37% were rural.

Regarding symptoms of hypocalcemia like muscle cramps or paresthesia, 95.9% of studied cases were asymptomatic. Forty cases (54.8%) had splenectomy while 33 cases (45.2%) had splenomegaly.

Table (1): Distribution of studied cases according to demographic and clinical data (N=73)

Variables		**N= 73**
Age (Mean ± SD)		26.2 ± 5.9
Sex: N (%)	Male	35 (45.5%)
	Female	38 (54.5%)
Marital Status: N (%)	Married	38 (54.5%)
	Single	35 (45.5%)
Residence: N (%)	Urban	46 (63%)
	Rural	27 (37%)
Symptoms: N (%)	Asymptomatic	70 (95.9%)
	Symptomatic	3 (4.1%)
Splenectomy: N (%)	Yes	40 (54.8%)
	No	33 (45.2%)
Splenomegaly: N (%)	Yes	33 (45.2%)
	No	40 (54.8%)

Table (2) illustrated that the mean age of first transfusion was 10.45 ± 5.9 months, while frequency of transfusion was 45 ± 15 days, the mean age of iron chelation was 19.31 ± 7.8 years, only 49.3% were compliant to treatment.

It showed also that mean ferritin level was 1329.3 ± 596.6, the prevalence of hypoparathyroidism among thalassemic patients was 24.7% while the prevalence of hypocalcemia among them was 20.5%.

Table (2): Distribution of studied cases according to transfusion, chelation therapy and laboratory data (N=73)

Variables		**N= 73**
Age of first transfusion (Mean ± SD) in months		10.45 ± 5.9
Frequency of blood transfusion (Mean ± SD) in days		45 ± 15
Age of iron chelation (Mean ± SD) in years		19.31 ± 7.8
Compliance to treatment N (%)	Compliant	36 (49.3%)
	Not compliant	37 (50.7%)
Ferritin (Mean ± SD)		1329.3 ± 596.6
PTH (Mean ± SD)		35.48 ± 4.46
Total Calcium (Mean ± SD)		8.96 ± 0.85
Ionized Calcium (Mean ± SD)		3.60 ± 0.17
Hemoglobin (Mean ± SD)		6.1 ± 2.7
TLC (Mean ± SD)		18.2 ± 3.1
Platelets (Mean ± SD)		315.5 ± 50.1
Hypoparathyroidism N (%)	Yes	18 (24.7%)
	No	55 (75.3%)
Hypocalcemia N (%)	Yes	15 (20.5%)
	No	58 (79.5%)

The mean age of patients with HPT was significantly higher (28.3 ± 5.4 years) than that of patients without HPT (24.1 ± 5.9years), while there were insignificant differences between both groups as regards sex, marital status, and residence ($p > 0.05$). There were insignificant differences between both groups as regards splenectomy and splenomegaly ($p > 0.05$).

Also, there were significant differences between both groups as regards compliance to treatment with oral iron chelators like Deferasirox of 20 mg/kg/day ($p < 0.05$). The mean age of patients with HPT was significantly higher (28.3 ± 5.4 years) than that of patients without HPT (24.1 ± 5.9years), while there were insignificant differences between both groups as regards sex, marital status, and residence ($p > 0.05$).

There were insignificant differences between both groups as regards splenectomy and splenomegaly ($p > 0.05$).

Also, there were significant differences between both groups as regards compliance to treatment with oral iron chelators like Deferasirox of 20 mg/kg/day ($p < 0.05$) as shown in table (3).

Table (3): Comparison between thalassemic patients with hypoparathyroidism and thalassemic patients with normal parathyroid hormone as regards demographic data and clinical data

Variables		Thalassemic patients with Hypoparathyroidism (n=18)	Thalassemic patients with normal parathyroid hormone (n=55)	Test	P-value
Age (Mean ± SD)		28.3 ± 5.4	24.1 ± 5.9	**6.12**	**0.04***
Sex N (%)	Male	10 (55.6%)	25 (45.5%)	0.91	0.39
	Female	8 (44.4%)	30 (54.5%)		
Marital Status N (%)	Married	9 (50%)	26 (47.3%)	1.19	1.21
	Single	9 (50%)	29 (52.7%)		
Residence N (%)	Urban	12 (66.7%)	34 (61.8%)	1.15	1.23
	Rural	6 (33.3%)	21 (38.2%)		
Splenectomy N (%)	Yes	10 (55.6%)	30 (54.5%)	0.81	1.32
	No	8 (44.4%)	25 (45.5%)		
Splenomegaly N (%)	Yes	8 (44.4%)	25 (45.5%)	0.98	1.65
	No	10 (55.6%)	30 (54.5%)		
Age of first transfusion (Mean ± SD)		9.9 ± 5.1	10.6 ± 6.1	1.32	0.41
Frequency of blood transfusion (Mean ± SD)		35.25 ± 10.32	42.71 ± 9.54	1.65	0.12
Age of iron chelation (Mean ± SD)		18.9 ± 6.2	20.1 ± 5.2	1.71	0.21
Compliance to treatment N (%)	Compliant	2 (11.1%)	34 (61.8%)	**6.32**	**0.001***
	Not compliant	16 (88.9%)	21 (38.2%)		

In table (4), we found that levels of PTH, total Ca, and Ca^{++} were significantly lower, while ferritin concentration was significantly higher in thalassemic patients with hypoparathyroidism.

Table (4): Comparison between thalassemic patients with hypoparathyroidism and thalassemic patients with normal parathyroid hormone as regards laboratory data

Variables	**Thalassemic patients with Hypoparathyroidism (n=18)**	**Thalassemic patients with normal parathyroid hormone (n=55)**	**Test**	**P-value**
Ferritin (Mean ± SD)	1865.3 ± 16.8	1214.5± 42.6	**4.74**	**0.04***
PTH (Mean ± SD)	11.58 ± 3.61	31.29 ± 5.16	**6.98**	**0.001***
Total Calcium (Mean ± SD)	6.96 ± 0.45	9.5 ± 0.6	**5.14**	**0.03***
Ionized Calcium (Mean ± SD)	2.60 ± 0.52	4.8 ± 0.86	**4.65**	**0.02***
Hemoglobin (Mean ± SD)	6.50 ± 0.10	6.70 ± 0.3	1.32	0.91
TLC (Mean ± SD)	19.1 ± 2.5	17.2 ± 2.9	1.62	1.25
Platelets (Mean ± SD)	310.5 ± 52.1	320.5 ± 49.2	1.21	1.39

In table (5), there were significant differences between both groups as regards age of first transfusion, frequency of blood transfusion and compliance to treatment ($p < 0.05$).

Table (5): Comparison between thalassemic patients with low calcium levels and others with normal calcium levels as regards clinical data

Variables		Thalassemic patients with low calcium levels (n=15)	Thalassemic patients with normal calcium levels (n=58)	Test	P-value
Age of the first transfusion (Mean ± SD)		9.4 ± 5.9	11.9± 7.2	**3.21**	**0.02***
Frequency of blood transfusion (Mean ± SD)		49.21 ± 15.32	39 ± 10.32	**2.36**	**0.04***
Age of iron chelation (Mean ± SD)		14± 5.9	21.4 ± 4.8	1.13	0.87
Compliance to treatment N (%)	Compliant	3 (20%)	35 (60.3%)	**7.12**	**0.001***
	Not compliant	12 (80%)	23 (39.7%)		

In table (6), the logistic regression analysis illustrated that advanced age, compliance to treatment, and ferritin were significant risk factors for HPT. After correcting for the covariates, compliance to treatment, and ferritin remained an independent risk factor.

Table (6 a & b): The logistic regression analysis of demographic, therapeutic, and clinical characteristics for risk of hypoparathyroidism in thalassemic patients

6- a
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	Univariate Logistic Regression Analysis		
Parameters	**OR**	**95% CI**	**P**
Age	**5.1**	**1.1 - 23.3**	**0.03**
Age of the first transfusion	1.9	0.8 - 4.8	0.1
Frequency of transfusion	0.7	0.2 - 2.1	0.5
Age of iron chelation	**0.4**	**0.2 - 1**	**0.05**
Compliance to treatment	**0.1**	**0.03 - 0.3**	**< 0.001**
Splenectomy	0.2	0.03 - 1.2	0.08
Splenomegaly	2.1	0.6 - 7.4	0.2
Ferritin	**9.5**	**3.3 - 27.1**	**< 0.001**
Hemoglobin	12.2	1.5 - 96.2	0.01
TLC	1.7	0.6 - 4.9	0.2
Platelets	2.5	0.7 - 8.8	0.1

6- b

	Multivariate Logistic Regression Analysis		
Parameters	**OR**	**95% CI**	**P**
Age	1	0.1 - 11.1	0.9
Age of the first transfusion	0.9	0.1 - 5.4	0.9
Frequency of transfusion	5.8	0.2 - 124	0.2
Age of iron chelation	6	0.2 - 124.6	0.2
Compliance to treatment	**0.3**	**0.05 - 2.9**	**0.001**
Splenectomy	4.7	0.06 - 340	0.4
Splenomegaly	0.6	0.7 - 5.1	0.6
Ferritin	**6.5**	**1 - 39.2**	**0.04**
Hemoglobin	1.8	0.08 - 39.4	0.6
TLC	1	0.2 - 4.3	0.9
Platelets	1.2	0.1 - 7.7	0.8

DISCUSSION

A hereditary condition called thalassaemia is brought on by aberrant haemoglobin. It causes peripheral haemolysis and inadequate erythropoiesis. Patients suffering from moderate to severe thalassaemia will inevitably require frequent blood transfusions [11].

Our research is predicated on the observation that certain HPT cases will persist even with the finest care for individuals with thalassaemia major. Since the majority of patients have no symptoms, it is crucial to aggressively search for them beginning in the early second decade of life in order to start therapy as soon as possible. The development of HPT is significantly influenced by inadequate chelation after repeated blood transfusions [16]. Although hypoparathyroidism is known to occur in people with thalassaemia major, it is believed to be rare and that its frequency is declining as chelation treatment advances [17]. This may be partially explained by the delay in initiating chelation therapy and treatment noncompliance. In our study, the prevalence of hypoparathyroidism among thalassemic patients was 24.7%, while the prevalence of hypocalcaemia among thalassemic patients was 20.5%.

Iron buildup in the parathyroid glands is thought to be the cause of HPT in thalassaemia. Iron excess has been linked to glandular damage through a number of potential pathways. These include many surface transferrin receptors in the cell, the production of free radicals and lipid peroxidation that damages the mitochondrial, lysosomal, and sarcolemma membranes, and the cell's defenses against inorganic iron [16]. According to **Mostafavi *et al.*** [18] and **Adil *et al.*** [19], hypoparathyroidism was found in 22.7% and 35.3% of thalassemic patients, respectively, in earlier research. The largest investigation on endocrine issues in thalassaemia, **DeSanctis *et al.*** [20], had 1861 patients from 25 centers and found that 3.6% of patients had HPT, however the rate varied from center to center.

According to the **Aleem *et al.*** [8] study, the reason why some patients acquire HPT while others do not is precisely understood. This is the case for the 20% of HPT in the thalassemic group. Additionally, 14.2% of patients in the **Razavi *et al.*** [21] research exhibited hypoparathyroidism. According to research by **Azami *et al.*** [22] conducted in Iran, 10% of individuals with thalassaemia major had hypoparathyroidism overall. Additionally, investigations by **Shamshirsaz *et al.*** [23], **Gamberini *et al.*** [24], and **Canatan** [25] found that the incidence of hypoparathyroidism in transfusion-dependent thalassaemia ranged from 0.5 to 7.6%. The main cause of its predominance was overt or symptomatic hypoparathyroidism. However, the **Tangngam *et al.*** [11] investigation found that 38% of transfusion-dependent thalassaemia patients had hypoparathyroidism, indicating a significant frequency of undiagnosed, asymptomatic hypoparathyroidism. Additionally, 49% of participants in the **Shah** [26] trial had hypocalcaemia.

Compared to patients without HPT (24.1 ± 5.9 years), patients with HPT had a considerably higher mean age (28.3 ± 5.4 years). However, sex, marital status, and place of residence did not significantly differ between the two groups ($p > 0.05$). **Manne *et al.*** [17] found that patients with HPT were considerably older (15.1 ± 5.8) than those without (9.2 ± 4.2 years). The average age of those with positive hypoparathyroidism in **Shah's** [26] research was 13.84 ± 3.98 years. The average age of patients with thalassaemia major and hypoparathyroidism in the **Azami *et al.*** [22] research was above 15, and more patients were older than 10. In their multicenter investigation, **DeSanctis *et al.*** [20] discovered that, with the exception of one, all thalassaemia patients who had HPT were older than ten years old. They came to the conclusion that HPT is mostly a condition that affects people in their second decade of life.

In our study, the group with hypoparathyroidism had considerably more symptomatic individuals than the group with normal thalassemic status ($p < 0.001$). However, splenectomy and splenomegaly did not significantly differ between the two groups ($p > 0.05$). 37.5% of hypoparathyroidism individuals in the **Razavi *et al.*** [21] research exhibited clinical signs of hypocalcaemia. Hypoparathyroidism was statistically significantly associated with diabetes, splenectomy, and desferal treatment. According to the **Grundy *et al.*** [27] study, even with the best care for patients with thalassaemia major, some HPT cases will still occur. Since the majority of patients have no symptoms, it is crucial to actively search for them beginning in the early second decade of life so that treatment can begin right away. If bone marrow transplantation (BMT) helps avoid endocrinopathies (This will be determined by longer follow-ups), this would be an additional argument in favor of BMT, particularly for patients who do not comply with desferal treatment.

According to the findings of our study, there were notable variations in the two groups' levels of treatment compliance. A person's sensitivity to iron toxicity or early parathyroid gland damage before chelation had decreased iron overload could be the cause of the non-significant differences in haemoglobin levels, serum ferritin, and transfusion and chelation therapy between those who had HPT and those who did not in **Manne *et al.*** [17] study. Clearly, some individuals will still acquire HPT even when appropriate chelation treatment lowers the incidence of HPT and other endocrine problems [16]. According to **Grundy *et al.*** [27] it might be challenging to persuade parents to begin chelation treatment. Lens opacification is one of the several adverse effects of desferal, and it's crucial to remember that HPT might result in cataract development. Hypocalcaemia in

thalassemic individuals can cause or worsen heart failure since many of them have compromised cardiac function.

In this investigation, thalassemic individuals with hypoparathyroidism had considerably greater ferritin concentrations and significantly lower levels of PTH, Ca, and Ca++. Similarly, 40 BTM patients and 15 controls with ages ranging from 2 to 18, were evaluated by **Shetty and Shenoy** [16]. They found that patients with b-thalassemia had significantly higher levels of blood phosphorus and alkaline phosphatase and significantly lower levels of PTH and serum calcium. They looked at every case where the parathyroid gland function was damaged, as seen by low serum calcium levels and high serum phosphorus levels. The balanced effects of PTH, vitamin D, and, to a lesser extent, calcitonin is necessary to maintain normal blood calcium content. The mainstay of treatment, vitamin D has a limited therapeutic range and is a long-acting medication. The creation of methods for measuring metabolites in plasma and determining the function of vitamin D in both normal and aberrant physiology is necessary for the current advancement in the field. Both the illness and the treatment have permanent side effects.

Contrary to the **Tangngam *et al.*** [11] research, which found that patients with hypoparathyroidism had a lower median blood ferritin level than those with normoparathyroidism, the patients in that study had a somewhat increased median serum ferritin level of 1333 ng/mL. Recent further iron chelation therapy with oral deferiprone and deferasirox can explain this result. With this medication, iron chelation significantly improved, which led to a quick drop in serum ferritin. Nonetheless, tissue iron buildup could continue to some extent. When desferrioxamine injection was the only treatment for transfusion-dependent thalassemic patients in previous years, serum ferritin levels were higher than 3,000 ng/mL [28]. Low serum calcium and high serum phosphorus levels, which indicate impairment to the parathyroid gland function, were seen in 27% of the individuals in the **Manne *et al.*** [17] investigation. The balanced effects of PTH, vitamin D, and, to a lesser extent, calcitonin is necessary to maintain a normal blood calcium content.

Our study's logistic regression analysis revealed that ferritin, advanced age, and medication compliance were important risk variables for HPT. Ferritin and treatment compliance remained independent risk factors after controlling for the covariates. According to some publications, HPT was linked to TM patients' ages, which is consistent with these findings [29], but other research did not support this association [24], as most HPT patients had inconsistent iron chelation. According to **Olivieri and Brittenham** [30], 22% of their thalassaemia patients experienced endocrine problems, as evidenced by a serum ferritin level more than 2000 µg/l. Studies by **Zandian *et al.*** [31], **Sleem *et al.*** [29] and **Belhoul *et al.*** [32] showed that elevated serum ferritin levels were linked to hypoparathyroidism in transfusion-dependent thalassaemia. It has been shown that a higher incidence of hypoparathyroidism is linked to a serum ferritin level more than 2,500–3,000 ng/mL. Furthermore, **Belhoul *et al.*** [32] found that the risk of developing hypoparathyroidism was 3.27 times higher for individuals whose blood ferritin levels were between 2,500 and 3,000 ng/mL. But according to **Shetty and Shenoy** [16] and **Angelopoulos *et al.*** [14] there is no known connection between serum ferritin and hypoparathyroidism. Additionally, they showed that tissue iron excess may not always be accurately detected by serum ferritin. According to **Porter *et al.*** [33] the quantity of iron from PRC transfusion may more accurately represent tissue iron buildup in individuals receiving poor iron chelation treatment. Therefore, while having lower blood ferritin levels, **Tangngam *et al.*** [11] found that individuals with hypoparathyroidism had higher cumulative iron loading than the normo-parathyroid patients. Iron buildup in the parathyroid glands is most likely the cause of hypoparathyroidism [34].

Given the explanation above, it would seem reasonable to assume that individuals with elevated serum ferritin levels are more likely to experience endocrine issues. The results from an Italian study by **De Satictis *et al.*** [35] supports this theory, although other researchers did not find any such association. Twenty-four BTM and HPT instances of varying severity were noted. When HPT was discovered, they were 16.5 years old on average (11–24 years old). The **Aleem *et al.*** [8] study, which contradicts our findings, also finds no strong link between serum ferritin levels and the onset of HPT. However, the study's sample size is small, and individual readings at diagnosis are most likely less significant than mean ferritin levels over longer time periods. **Grundy *et al.*** [27] discovered that individuals with thalassaemia who can maintain serum ferritin levels below 2500 µg/L had the highest chance of surviving. Nonetheless, some patients who get optimal care according to current standards do experience serious endocrine impairment.

Serum ferritin levels below 2000 µg/L were reported in 22% of thalassaemia patients with endocrine problems, according to a multicenter investigation by **DeSanctis *et al.*** [20]. Therefore, it makes perfect sense to assume that organ damage may also be caused by other circumstances. Individual susceptibility to iron damage, elevated collagen deposition due to elevated activity of the iron-dependent proto-collagen proline hydroxylase enzyme, which subsequently disrupts parathyroid and pancreatic microcirculation, and chronic anaemia are some of the several processes.

Limitations: This study had several drawbacks. The sample size was tiny to start. Second, there was no

measurement of serum 1.25-(OH)2 vitamin D or FGF-23. Therefore, it was not possible to evaluate the pathophysiological alterations in serum 1.25-(OH)2 vitamin D linked to plasma FGF-23 during hypoparathyroidism or normoparathyroidism.

CONCLUSION

In conclusion, transfusion-dependent beta-thalassemia major patients frequently experience subclinical hypoparathyroidism and hypocalcaemia, which may be brought on by poor adherence to iron chelation therapy and older age. In individuals with iron overload, hypocalcaemia is often asymptomatic and persistent. Furthermore, our results suggested the need for routine screening of parathyroid function and serum calcium levels that is crucial for early detection and management of these complications. Comprehensive care strategies, including regular monitoring, patient education, and tailored interventions, are needed to improve long-term outcomes and quality of life for β-TM patients. Future research should explore the underlying mechanisms of HPT development and evaluate targeted approaches to prevent its onset.

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REFERENCES

1. **Majumder A, Basu S (2020):** Hypoparathyroidism in a case of transfusion dependent thalassemia. Journal of the ASEAN Federation of Endocrine Societies, 35 (1): 129.
2. **Mohammadian S, Bazrafshan U, Sadeghi-Nejad A (2003):** Endocrine Gland Abnormalities in Thalassemia Major: Λ Brief Review. Journal of Pediatric Endocrinology and Metabolism, 16 (7): 957-964.
3. **Vogiatzi M, Macklin E, Trachtenberg F *et al.* (2009):** Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. British journal of haematology, 146 (5): 546-556.
4. **Gabriele O (1971):** Hypoparathyroidism associate with thalassemia. Southern Medical Journal, 64 (1): 115-116.
5. **Even L, Bader T, Hochberg Z (2007):** Nocturnal calcium, phosphorus and parathyroid hormone in the diagnosis of concealed and subclinical hypoparathyroidism. European journal of endocrinology, 156 (1): 113-116.
6. **Strain J, Cashman K (2009):** Minerals and trace elements. Introduction to human nutrition, 188: 192
7. **Pepe J, Colangelo L, Biamonte F *et al.* (2020):** Diagnosis and management of hypocalcemia. Endocrine, 69: 485-495.
8. **Aleem A, Al-Momen A, Al-Harakati M *et al.* (2000):** Hypocalcemia due to hypoparathyroidism in β-thalassemia major patients. Annals of Saudi medicine, 20 (5-6): 364-366.
9. **Janett S, Camozzi P, Peeters G *et al.* (2015):** Hypomagnesemia induced by long-term treatment with proton-pump inhibitors. Gastroenterology research and practice, 21: 951768.
10. **Demeester-Mirkine N, Hooghe L, Van Geertruyden J, De Maertelaer V (1992):** Hypocalcemia after thyroidectomy. Archives of surgery, 127 (7): 854-858.
11. **Tangngam H, Mahachoklertwattana P, Poomthavorn P *et al.* (2018):** Under-recognized hypoparathyroidism in thalassemia. Journal of clinical research in pediatric endocrinology, 10 (4): 324.
12. **Dawson B, Trapp R (2004):** Basic & clinical biostatistics. InBasic & clinical biostatistics, Pp: 438-438. https://www.scirp.org/reference/referencespapers?referenceid=1520407
13. **Ciosek Ż, Kot K, Kosik-Bogacka D *et al.* (2021):** The effects of calcium, magnesium, phosphorus, fluoride, and lead on bone tissue. Biomolecules, 11 (4): 506.
14. **Angelova P, Choi M, Berezhnov A *et al.* (2020):** Alpha synuclein aggregation drives ferroptosis: an interplay of iron, calcium and lipid peroxidation. Cell Death & Differentiation, 27 (10): 2781-2796.
15. **Hsu C, Senussi N, Fertrin K, Kowdley K (2022):** Iron overload disorders. Hepatology communications, 6 (8): 1842-1854.
16. **Shetty B, Shenoy U (2014):** Prevalence of hypoparathyroidism (HPT) in beta-thalassemia major. Journal of Clinical and Diagnostic Research, 8(2):24.
17. **Manne N, Yadav S, Gupta B *et al.* (2020):** Prevalence of hypoparathyroidism, growth retardation in patients of β-thalassemia major. Age, 10: 25.
18. **Mostafavi H, Afkhamizadeh M, Rezvanfar M (2005):** Endocrine disorders in patients with thalassemia major. Iranian Journal of Endocrinology and Metabolism, 7 (2): 143-147.
19. **Adil A, Sobani Z, Jabbar A *et al.* (2012):** Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan. Journal of the Pakistan Medical Association, 62 (3): 307.
20. **De Sanctis V, Soliman A, Canatan D *et al.* (2017):** An ICET-A survey on Hypoparathyroidism in Patients with Thalassaemia Major and Intermedia: A preliminary report. Acta Bio Medica: Atenei Parmensis, 88 (4): 435.

21. **Razavi Z, Bazmamoun H, Saba M (2009):** The frequency of hypoparathyroidism in patients with Beta-thalassemia in Hamadan-Iran. Journal of Gorgan University of Medical Sciences, 10 (4): 29-91.
22. **Azami M, Parizad N, Sayehmiri K (2016):** Prevalence of hypothyroidism, hypoparathyroidism and thefrequency of regular chelation therapy in patients with thalassemia major in Iran: A systematic review and meta-analysis study. Iranian Journal of Pediatric Hematology and Oncology, 6 (4): 261-276.
23. **Shamshirsaz A, Bekheirnia M, Kamgar M *et al.* (2003):** Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC endocrine disorders, 3: 1-6.
24. **Gamberini M, De Sanctis V, Gilli G (2008):** Hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism: incidence and prevalence related to iron overload and chelation therapy in patients with thalassaemia major followed from 1980 to 2007 in the Ferrara Centre. Pediatric endocrinology reviews, 6: 158-169.
25. **Canatan D (2013):** The Thalassemia center of Antalya State Hospital: 15 years of experience (1994 to 2008). Journal of pediatric hematology/oncology, 35 (1): 24-27.
26. **Shah S (2015):** Assessment of serum calcium and phosphorus levels among transfusion-dependent beta thalassemia major patients on chelation therapy. Journal of Postgraduate Medical Institute, 29(3): 168-170
27. **Grundy R, Woods K, Savage M, Evans J (1994):** Relationship of endocrinopathy to iron chelation status in young patients with thalassemia major. Archives of disease in childhood, 71 (2): 128-132.
28. **Mahachoklertwattana P, Chuansumrit A, Sirisriro R *et al.* (2003):** Bone mineral density, biochemical and hormonal profiles in suboptimally treated children and adolescents with β-thalassaemia disease. Clinical endocrinology, 58 (3): 273-279.
29. **Sleem G, Al-Zakwani I, Almuslahi M (2007):** Hypoparathyroidism in adult patients with beta-thalassemia major. Sultan Qaboos University Medical Journal, 7 (3): 215.
30. **Olivieri N, Brittenham G (1997):** Iron-chelating therapy and the treatment of thalassemia. Blood, The Journal of the American Society of Hematology, 89 (3): 739-761.
31. **Zandian K, Mohammadian N, Riahy K *et al.* (2005):** The prevalence of hypoparathyroidism among patients with major thalassemia aged above 10 years. 157-164. https://pesquisa.bvsalud.org/portal/resource/pt/emr-71023
32. **Belhoul K, Bakir M, Saned M *et al*. (2012):** Serum ferritin levels and endocrinopathy in medically treated patients with β thalassemia major. Annals of hematology, 91: 1107-1114.
33. **Porter J, Viprakasit V, Kattamis A (2014):** Iron overload and chelation. InGuidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd edition. Thalassaemia International Federation. 42-56
34. **Habeb A, Al-Hawsawi Z, Morsy M *et al*. (2013):** Endocrinopathies in beta-thalassemia major. Prevalence, risk factors, and age at diagnosis in Northwest Saudi Arabia. Saudi medical journal, 34 (1): 67-73.
35. **De Sanctis V, Vullo C, Bagni B, Chiccoli L (1992):** Hypoparathyroidism in beta-thalassemia major. Clinical and laboratory observ-ations in 24 patients. Acta haematologica, 88 (2-3): 105-108.