Research Paper

Investigating the Relationship Between Parathyroid Hormone Levels and Depression and Anxiety in Patients With Transfusion-dependent Thalassemia

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ABSTRACT

Background and Objective: Thalassemia is characterized by impaired synthesis of hemoglobin chains, leading to chronic anemia. Patients with thalassemia require blood transfusions for survival. Chronic blood transfusions lead to complications arising from iron deposition in various organs. Hypoparathyroidism is a complication of blood transfusion in patients with thalassemia. It has been observed that hypoparathyroidism is associated with psychological complications, including depression.

Materials & Methods: In this study, all patients with transfusion-dependent thalassemia (TDT) who were referred to the Thalassemia Clinic of Bou-Ali Hospital in Sari City, Iran, in 2023 and met the inclusion criteria were enrolled. Depression and anxiety were assessed using the hospital anxiety and depression scale (HADS). The levels of parathyroid hormone (PTH), Vitamin D, calcium, and phosphorus were recorded for all patients. The data were analyzed using Stata software, version 13 with t-tests, analysis of variance, and multiple regressions.

Results: Of the 204 patients examined, 107(52.5%) were female. The mean Vitamin D level was 33.40±10.12 ng/mL, and the mean PTH level was 28.46±9.71 ng/mL. The levels of Vitamin D, calcium, phosphorus, and PTH were not significantly correlated with anxiety (P=0.33, P=0.30, P=0.28, and P=0.21, respectively). Similarly, none of the four variables under consideration were significantly associated with depression (P=0.92, P=0.85, P=0.96, and P=0.77, respectively).

Conclusion: Despite previous studies indicating a correlation between PTH levels and depression, this study demonstrated no significant association between the mean serum levels of Vitamin D, calcium, phosphorus, and PTH with depression and anxiety in patients with TDT.

Keywords: Thalassemia, Depression, Anxiety, Parathyroid hormone (PTH)

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Introduction

Thalassemia is a hereditary blood disorder characterized by reduced hemoglobin production, leading to mild-to-severe anemia [1]. Mutations in the beta-globin gene result in inappropriate synthesis of the beta-globin protein, leading to an imbalance between the alpha and beta-globin chains. Free alpha chains accumulate in red blood cells, leading to beta-thalassemia [2].

Thalassemia syndrome is classified based on clinical manifestations and the need for blood transfusions. Inappropriate hemoglobin production results in ineffective erythropoiesis and increased peripheral hemolysis [3]. Iron overload resulting from repeated transfusions causes complications and mortality in transfusion-dependent patients.

Excess iron is often deposited in the liver, heart, and endocrine system [3, 4]. In patients with transfusion-dependent thalassemia (TDT), frequent blood transfusions and iron overload lead to numerous endocrine complications, including hypogonadism, diabetes, hypothyroidism, and hypoparathyroidism [5].

Following iron deposition in the parathyroid glands, thalassemia patients become susceptible to hypoparathyroidism. Parathyroid hormone (PTH) is a polypeptide hormone secreted by the parathyroid gland [6]. Hypoparathyroidism is a hormonal disorder resulting from the absence or reduced blood level of PTH. Hypoparathyroidism leads to hypocalcemia, hyperphosphatemia, and hypercalciuria [7].

The reported prevalence of hypoparathyroidism in patients with TDT ranges from 4% to 40% [8]. Hypoparathyroidism affects various body systems, including the kidneys, nerves, psyche, skeleton, and immune system, with neuropsychiatric complications being among the most significant [9, 10].

The rate of neuropsychiatric complications, including depression, has been reported to be higher in patients with non-surgical hypoparathyroidism than in healthy individuals [11].

Approximately 320,000 children are born annually with hemoglobinopathies, and nearly 80% of these births occur in developing countries [12]. Patients with thalassemia are exposed to psychological consequences that affect disease progression and both short- and long-term outcomes [13].

Depression and anxiety are prevalent in thalassemia patients, with their prevalence significantly higher than in the general population. Studies have shown that up to 80% of patients with thalassemia may experience some degree of mental disorders. Psychosocial factors, such as recurrent hospitalizations, comorbidities (such as diabetes and heart failure), short stature, and delayed puberty, are among the most significant predictors of these disorders [14, 15].

In patients with thalassemia, disturbances in calcium, phosphorus, Vitamin D, and PTH metabolism are very common. Vitamin D deficiency, hypocalcemia, hyperphosphatemia, and elevated PTH occur due to chronic iron loading, liver damage, and endocrine disorders. These disturbances lead to decreased bone mineral density and an increased risk of fracture. Iron overload and liver damage play key roles in these disturbances, and their severity increases with age and disease severity [16, 17].

There is substantial evidence linking Vitamin D deficiency to increased depression and anxiety in both the general population and patients with thalassemia. Vitamin D acts as a neurosteroid that regulates brain function and mood, and its deficiency is associated with increased symptoms of depression and anxiety. Furthermore, elevated PTH has been associated with cognitive impairment and depression [18, 19]; studies have indicated that individuals with higher PTH levels have poorer cognitive function and higher depression scores. Calcium and phosphorus disturbances can also affect mental health and sleep quality; specifically, hypocalcemia and phosphorus abnormalities are associated with increased anxiety and sleep disturbances [19, 20].

Despite numerous studies in this area, the direct relationship between PTH levels and depression and anxiety in these patients has been less explored. Identifying this relationship can lead to a better understanding of the biological mechanisms affecting psychiatric disorders and aid in designing more targeted therapeutic interventions. Therefore, this study aimed to investigate the relationship between PTH levels and depression and anxiety in patients with thalassemia to contribute to integrated biological and psychological interventions for these patients.

Materials and Methods

Study design and setting

This analytical cross-sectional study included patients with TDT who were actively referred to the Thalassemia Ward of Bou-Ali Hospital in Sari City, Mazanda-

ran Province, Iran, for blood transfusions at least once monthly in 2023.

Sample size calculation

The standard formula (Equation 1) for comparing the means of two independent groups was utilized to calculate the required sample size. The parameters employed in this formula were identical to those used in a previous study [21]:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \cdot (S_1^2 + S_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

1. $$n = \frac{(1.96 + 0.84)^2 \times (3.17^2 + 3.17^2)}{(7.42 - 6.40)^2} =$$

$$\frac{7.84 \times 20.0978}{1.0404} \approx 151.7$$

Considering the possibility of incomplete or missing responses, a 20% attrition rate was assumed, leading to a preliminary final sample size of 190 individuals. To enhance precision and patient accessibility, the final sample size for the current study was set at 204 participants, exceeding the minimum required.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

1) Diagnosis of TDT; 2) Age e 18; 3) Absence of any severe emotional stressor within the preceding three months (e.g. fatal accident, bereavement, or divorce); 4) Absence of severe comorbidities, including pulmonary hypertension, liver or kidney failure, chronic diseases such as cancer, significant cognitive impairment, mental retardation, or current substance use (drugs or stimulants).

The exclusion criteria were as follows:

Incomplete medical records lacking the data required for this study; 2) refusal to provide informed consent for participation; and 3) failure to undergo the required laboratory assessments for serum levels of PTH, calcium, phosphorus, and vitamin D.

Data collection and assessment tools

Information regarding the use of psychotropic medications, tobacco (cigarettes), and alcohol was systematically recorded. After written informed consent was obtained, a comprehensive demographic questionnaire was administered. This questionnaire collected data on: age, gender, marital status, presence of other physical comorbidities, history of psychiatric illness, current psychiatric medication use, annual frequency of hospital visits, and status of PTH, calcium, phosphorus, and Vitamin D levels, as well as the total number of blood transfusions received.

Psychiatric symptoms were evaluated using the hospital anxiety and depression scale (HADS). All necessary laboratory tests were conducted free of charge at the Bou-Ali Hospital Laboratory, utilizing identical methods and equipment for standardization.

The HADS questionnaire consists of 14 items, divided into two independent subscales: anxiety and depression. Each item was scored on a scale of 0-3. The total score for each subscale ranged from 0 to 21. The following thresholds were used to categorize the severity for both the anxiety and depression subscales:

Normal: ≤7; Mild: 8−10; Modeate: 11−14; Severe: 5−21

The validity and reliability of the HADS in the Iranian population have been previously confirmed, with reported Cronbach's α values of 0.78 for anxiety and 0.86 for depression [22]. The questionnaires were self-administered by the patients under the direct supervision of the research student.

Grouping based on HADS scores

The completed HADS questionnaires allowed for the division of patients into two main categories: depressed vs. non-depressed, and anxious vs non-anxious. Patients scoring ≤7 were categorized as non-depressed, while those scoring >7 were categorized based on their score into mild, moderate, or severe depression. Similarly, patients with scores ≤7 were grouped as non-anxious, while those with scores >7 were categorized into mild, moderate, or severe anxiety groups. The measured levels of PTH, Vitamin D, calcium, and phosphorus for all patients were recorded from their files and subsequently compared and analyzed.

Statistical analysis

After the study was completed, the data were compiled. Statistical analyses and interpretations were then performed using STATA software, version 13. Descriptive statistics, such as Mean±SD, were used if the primary outcome demonstrated a normal distribution; otherwise, the median and interquartile range (IQR) were employed.

In addition to comparing the serum levels of PTH, Vitamin D, calcium, and phosphorus between patients with depression/anxiety and those without, the percentage of patients with hypoparathyroidism was compared between these two groups. Simple linear regression was used to examine the association between depression/anxiety and PTH. The independent t-test and analysis of variance were employed for group mean comparisons, and multiple linear regression was used to control for potential confounding variables.

Results

Based on Table 1, the mean age of the participants in our study was 36.13±6.17 years. Of the 204 patients examined, 107 (52.5%) were female. The number of married individuals (126; 61.8%), was higher than that of single and divorced individuals. Furthermore, 58 participants (28.4%) had an education level below a diploma, and 146 participants (71.6%) had diplomas or higher.

Additionally, among the study participants, 32 individuals (15.84% of the 204 participants) reported a history of smoking. Only six individuals mentioned alcohol consumption.

According to Table 2, in our study, 47 individuals (23.0%) experienced anxiety, of whom only 9 (4.4%) reported severe anxiety, and 22 (10.8%) reported mild anxiety. The prevalence of depression in the studied sample was 48 individuals (23.5%), where, similar to anxiety, 9 (4.4%) had severe depression, 19 (9.3%) had mild depression, and the remainder had moderate depression. The mean anxiety score was 50.5±4.25, with the highest score being 19. The mean depression score in the sample was low at 40.7±4.60.

Based on Table 3, the mean level of Vitamin D was 33.40±10.12 ng/mL, and the mean level of PTH in the study was 28.46±9.71 ng/mL. The minimum and maximum PTH values were 1.2 and 41 ng/mL, respectively.

Individuals were divided into two groups: those with and those without depression, and the mean levels of Vitamin D, calcium, phosphorus, and PTH were examined. None of the four factors under consideration showed a statistically significant difference with depression (P=0.92, P=0.85, P=0.96, P=0.77).

Based on Table 4, in the investigation of the relationship between the mean levels of Vitamin D, Calcium, Phosphorus, and PTH and anxiety, no significant differences were found between anxiety and the variables under consideration (P=0.33, P=0.30, P=0.28, P=0.21).

Table 1. Demographic characteristics of studied patients

Characteristic		No. (%)
Gender	Male	97(47.5)
	Female	107(52.5)
Marital status	Single	71(34.8)
	Married	126(61.8)
	Divorced/separated	7(4.3)
Education Level	Below diploma	58(28.4)
	Diploma and associate degree	77(37.7)
	Bachelor's degree	50(24.5)
	Master's degree	19(9.3)
	Total	204(100)

Characteristic	Mean±SD	Min	Max
Age of study participants	13.36±17.6	19	62

Table 2. Assessment of anxiety and depression in study participants

Characteristic			No. (%)
Anxiety	Yes	Mild	22(10.8)
		Moderate	16(7.8)
		Severe	9(4.4)
		Total	47(23.0)
	No		157(77.0)
Depression	Yes	Mild	19(9.3)
		Moderate	20(9.8)
		Severe	9(4.4)
		Total	48(23.5)
	No		156(76.5)

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To simultaneously investigate the effects of biochemical and demographic variables, two multiple regression models were used to predict the depression and anxiety scores.

According to Table 5, based on the multiple regression results, none of the variables—Vitamin D, Calcium, Phosphorus, age, gender, or marital status—showed a significant association with either depression or anxiety.

The Beta coefficients and R^2 values were 0.06 for depression and 0.05 for anxiety. These values indicate that the evaluated variables play a small role in explaining the variance of depression and anxiety. Beta represents the regression coefficient, and SE represents the standard error.

Discussion

Patients with thalassemia are exposed to psychological consequences that affect the course of the disease and its short- and long-term outcomes [13].

Based on various studies, the prevalence of psychiatric disorders in patients with thalassemia is reported to be between 25% and 30% [12]. Hypoparathyroidism is a complication of blood transfusions in patients with TDT. According to existing studies, hypoparathyroidism can lead to the onset of neuropsychiatric symptoms, including depression. Given the high prevalence of psychiatric disorders in patients with thalassemia and the significant

Table 3. Relationship between vitamin d, calcium, phosphorus, PTH, and depression

Characteristic	Depression	No.	Mean±SD	P
Vitamin D (ng/mL)	No	156	33.37±10.26	0.92
	Yes	48	33.52±9.78	
Calcium (mg/dL)	No	156	9.17±0.71	0.85
	Yes	48	9.15±0.68	
Phosphorus (mg/dL)	No	156	4.70±0.82	0.96
	Yes	48	4.71±0.78	
PTH (ng/mL)	No	156	28.57±9.89	0.77
	Yes	48	28.10±9.21	

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Table 4. Relationship between vitamin D, calcium, phosphorus, PTH, and anxiety

Characteristic	Anxiety	No.	Mean±SD	P
Vitamin D (ng/mL)	No	157	33.03±10.50	0.33
	Yes	47	34.66±8.73	
Calcium (mg/dL)	No	157	9.19±0.73	0.30
	Yes	47	9.07±0.62	
Phosphorus (mg/dL)	No	157	4.67±0.83	0.28
	Yes	47	4.82±0.72	
PTH (ng/mL)	No	157	28.92±9.90	0.21
	Yes	47	26.90±8.98	

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Table 5. Simultaneous association of biochemical variables with depression and anxiety

Variables	Depression		Anxiety	
	Beta±SE	P	Beta±SE	P
PTH	0.012±0.014	0.413	-0.015±0.016	0.362
Vitamin D	0.007±0.013	0.586	0.014±0.013	0.296
Calcium	0.09±0.09	0.329	0.07±0.08	0.402
Phosphorus	0.06±0.08	0.441	0.05±0.07	0.481
Age	0.03±0.02	0.238	0.02±0.02	0.242
Gender	0.48±0.42	0.267	0.51±0.39	0.193
Marital status	0.39±0.36	0.285	-0.42±0.34	0.220

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role of biopsychosocial factors in the development of psychiatric symptoms, this study aimed to investigate the relationship between the level of PTH, which is a crucial biological factor, and depression and anxiety in patients with TDT.

In the present study, depressive symptoms were observed in 23% of the patients, with moderate and severe depression reported in 15% of the patients. This is a significantly lower percentage than that reported by Zolaly et al. [23]. Zolaly's study involved 62 patients and used the Depression, Anxiety and Stress Scale-21 Items (DASS-21) assessment tool; the smaller sample size and different assessment tool may account for the difference in results. Notably, our findings are consistent with the prevalence reported internationally [24–26]. In the analysis performed, patients with thalassemia did not show very high anxiety scores. The mean scores for both sections of the questionnaire (5.50 in the anxiety section and 4.70 in the depression section) were less than 7, indicating normality (individuals scoring below 7 were considered normal, and those scoring above 7 were considered anxious or depressed). However, there were notably severe cases in the study, with the highest anxiety and depression scores being 19 out of 21.

Anxiety was diagnosed in 23.5% of our patients, with severe anxiety in approximately 4.4% and moderate anxiety in 7.8% [23]. Several studies have reported the prevalence of depression in patients with thalassemia, varying from 10% to 50%, with our study reporting this figure at 23.5% [21, 27, 28].

Various reports from Iran indicate that depression in thalassemia patients is a dominant manifestation, ranging between 12% and 30%, with up to 54% of patients suffering from some form of pathological mental disorder [23, 29, 30]. More serious psychological complications can occur in patients with thalassemia. One study in Iran reported that up to 27.3% of patients had contemplated suicide in the year preceding the study [31]. In Arab societies, a 2012 study reported similar findings in 80 patients in Lebanon, where 35% of the patients were depressed [32]. Al-Hakeim et al. reported that severe depression in children with thalassemia is strongly associated with the number of blood transfusions, iron overload, and increased levels of interleukin-1β [33]. In Saudi Arabia, a study on patients with sickle cell anemia in the Qatif region reported that 48% of the patients had depressive symptoms. This may suggest that all patients with hereditary hemoglobinopathies or other chronic medical diagnoses are at risk of developing mental disorders [34]. Adolescents with chronic medical diagnoses, such as thalassemia, are at higher risk for psychological disorders, such as identity problems and hormonal changes. However, children and older patients remain at risk for serious stress-related psychiatric and mental disorders associated with stress [21].

Hypoparathyroidism is well-recognized among blood transfusion-dependent β-thalassemia patients and is often observed in patients with higher iron stores, frequently accompanied by other endocrine disorders [35–37]. Acquired hypoparathyroidism resulting from hemosiderosis (due to repeated blood transfusions) is always the first consideration for hypocalcemia in patients with thalassemia. However, ferritin concentration is not a reliable predictor of hypoparathyroidism because many studies have reported no significant difference in serum ferritin levels between patients with and without hypoparathyroidism [38–40]. This study investigated the mean serum levels of Vitamin D, calcium, phosphorus, and PTH in relation to depression and anxiety.

A comparison of serum levels of Vitamin D, calcium, phosphorus, and PTH between depressed and non-depressed patients showed that none of the biochemical variables correlated significantly with depression (P=0.92, P=0.85, P=0.96, and P=0.77, respectively).

In examining the relationship of the above indicators with anxiety, no significant difference was observed between the two groups. The values were P=0.33 for Vitamin D, P=0.30 for calcium, P=0.28 for phosphorus, and P=0.21 for PTH.

To simultaneously investigate the effect of biochemical and demographic variables, two multiple regression models were used to predict the depression and anxiety scores. Based on the results of the multiple regressions, none of the variables—Vitamin D, calcium, phosphorus, age, gender, or marital status—showed a statistically significant association with either depression or anxiety.

The Beta coefficients and R^2 values were 0.06 for depression and 0.05 for anxiety. These values indicate that the evaluated variables explain very little variance in depression and anxiety. Regression assumptions, including normality of residuals, lack of multicollinearity (VIF <2), independence of errors, and homogeneity of variance, were checked and confirmed. Accordingly, the regression models were statistically valid, but their predictive power was weak.

The findings of this study contradict some previous studies that reported an association between high PTH or low Vitamin D levels and depression and anxiety. Based on this, the role of psychosocial factors and the burden and complications of chronic disease contribute more significantly than biological factors. The choice of assessment tools, sample size, disease severity, and other confounding factors may lead to these differing results.

Early diagnosis and appropriate support and management are highly needed to help patients cope with the illness and improve their quality of life. All patients with symptoms of depression, anxiety, or stress should be referred to a psychiatric clinic for appropriate intervention. Further studies with a long follow-up program and multicenter national registration are highly needed to optimize the appropriate care for these patients. Considering that the instruments for assessing depression and anxiety differ across various studies, different results are expected, and a semi-structured psychiatric interview may yield more comparable results. It is also recommended that future research utilize longitudinal studies and larger patient cohorts to establish a clearer causal relationship.

Conclusion

Despite prior studies suggesting a correlation between PTH levels and depression, this study found no significant association between the mean serum levels of vitamin D, calcium, phosphorus, or PTH and depression or anxiety in patients with TDT.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code: IR.MAZUMS.REC.1402.11700).

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Authors' contributions

Writing the manuscript: Maryam Rezapour and Soheil Shabanpour; Study design: Maryam Rezapour; Research: Hossein Karami; Data analysis: Mohammad Naderi Sorki; Data collection: Soheil Shabanpour.

Conflict of interest

The authors declared no conflicts of interest.

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