

Correlation of serum ferritin with parathyroid hormone level in patients with transfusion-dependent thalassemia



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ABSTRACT

Introduction: Thalassemia is a rare hereditary condition that causes hemoglobin synthesis deficiency. Recurrent blood transfusion in transfusion-dependent thalassemia (TDT) individuals results in iron overload and deposition in body tissues, leading to endocrine malfunctions, including parathyroid. This study aimed to determine the correlation between the level of serum ferritin and parathyroid hormone level in TDT patients.

Methods: A cross-sectional study was conducted among adult TDT patients receiving blood transfusions at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January to June 2023. Serum ferritin was measured using an enzyme-linked fluorescence assay (ELFA), while parathyroid hormone was quantified using an enzyme-linked immunosorbent assay (ELISA). The Spearman correlation analysis was used to identify the correlation between the level of serum ferritin with parathyroid hormone.

Results: A total of 46 TDT patients were enrolled in the study, with a median age of 25 years old and represented predominantly by males (56.5%). The median levels of serum ferritin and parathyroid hormone were 5,672.90 ng/mL (min-max: 596.80–24,014.58 ng/mL) and 29.80 pg/mL (min-max: 10.61–97.01 pg/mL), respectively. The Spearman correlation analysis suggested a statistically insignificant negative correlation between serum ferritin and parathyroid hormone in TDT patients ($r = -0.166$; $p = 0.270$).

Conclusion: Serum ferritin was inversely, but not significantly, correlated with parathyroid hormone in TDT patients, suggesting that impaired parathyroid function might be associated with the increment of plasma iron.

Keywords: Transfusion-dependent thalassemia, serum ferritin, parathyroid hormone, hemoglobin synthesis deficiency, iron overload.

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INTRODUCTION

Thalassemia is a rare genetic disorder of impaired hemoglobin synthesis due to imbalanced, reduced, or absent production of alpha or beta globin chains associated with globin gene mutations.¹⁻³ The prevalence of thalassemia varies greatly throughout the world and has a distribution history called the thalassemia belt.^{4,5} The prevalence of new symptomatic cases is estimated at approximately 60,000 people worldwide.^{5,6} In Indonesia, the prevalence of thalassemia ranges from 5–10%,⁷ and around 0–10% of the population carry β -thalassemia.⁴⁻⁸ Nearly half of the thalassemia sufferers are concentrated on Java Island, especially in Jakarta and West Java.^{9,10}

Patients with thalassemia surveillance rate depends greatly on adequate blood transfusions and control of excessive iron levels.^{3,4} With the presence of advanced therapy and acceleration in blood donation practice nowadays, mortality rates can be reduced.¹¹⁻¹³ However; this condition, in return, leads to an increase in morbidity rate owing to iron overload.^{4,14,15} Unresolved excess iron has been reported to affect various organs such as the heart, liver, and endocrine glands.¹⁶ Only 39% of nearly 100,000 patients with transfusion-dependent thalassemia (TDT) receive adequate iron chelating therapy worldwide, and approximately 3,000 of them die each year from iron overload-related complications.⁴ Data from the southeastern region of Iran shows that

40.7% of patients died by the age of 25 years.¹⁷

Multi-country reports suggested that hypogonadism, parathyroid dysfunction, and diabetes are the most common endocrine complications among thalassemia major patients receiving routine transfusions.¹⁸ The most frequent parathyroid dysfunction is hypoparathyroidism, which is considered a rare consequence of iron overload as a result of recurrent transfusions. Parathyroid dysfunction is considered a long-term complication and is more common after the age of 16 years.¹⁹ A recent study on endocrine disorders involving 1,861 thalassemia major patients from 25 different hospitals indicated that 3.6% was hypoparathyroidism.²⁰ Nevertheless,

in Indonesia itself, studies regarding thalassemia are still limited, particularly those focusing on the identification of the relationship between serum ferritin levels and parathyroid hormone in thalassemia patients. Serum ferritin has been considered a good marker of the total iron stores in the body, thus determination of serum ferritin levels is useful in the identification of iron status in the body.²¹ Hence, this study aimed at determining the correlation between serum ferritin and parathyroid hormone among TDT patients.

METHODS

Study design and sample collection

A cross-sectional study was carried out among TDT patients at Dr. Soetomo General Academic Hospital from January to June 2023. TDT is defined as thalassemia patients requiring a life-long blood transfusion, diagnosed through an anamnesis, clinical symptoms, complete blood test and blood smear, hemoglobin electrophoresis, high-performance liquid chromatography (HPLC), and DNA analysis.²² Patients ≥ 18 years of age, requiring blood transfusion every 2-5 weeks, and receiving blood transfusion >10 times in total were included in the study, whereas patients with infections, hepatitis B, hepatitis C, malignancy, chronic kidney disease, malabsorption, and obesity; alcoholics; pregnant women; and nursing mothers were excluded.

Study variables and data collection

The data used in this study was primary data, including serum ferritin as an independent variable and parathyroid hormone as a dependent variable. The level of serum ferritin was measured by an enzyme-linked fluorescence assay (ELFA) using a mini automated analyzer VIDAS (vitek immunodiagnostic assay system) (Biomérieux). The level of parathyroid hormone was quantified using an enzyme-linked immunosorbent assay (ELISA). Demographic and clinical characteristics of the patients, including age, gender, the number of transfusions, splenomegaly status, clinical symptoms, types of iron chelators taken, as well as a history of diseases, smoking, and alcohol consumption were also recorded. All the

patients were informed of the study and voluntarily signed informed consent prior to the study.

Statistical analysis

All data analyses were performed using SPSS software. Data on demographic and clinical characteristics were analyzed using descriptive statistics and presented as median (interquartile), mean \pm standard deviation (SD), and percentage (%). The Spearman correlation test was used to identify the association between the levels of serum ferritin and parathyroid hormone.

RESULTS

A total of 46 patients were included in the study. The demographic and clinical characteristics are presented in Table 1. The median age was 25 years and more than half of the patients were males (56.5%). The median quantity of transfused red blood cells (RBC) was 2 units per month, and the median spleen enlargement (Scuffner scale) was 2. Fatigue (62.7), weight loss (13.7%), and heart palpitations (11.8%) were among the most common clinical symptoms. More than half of the patients received deferasirox for iron chelation (56.6%); however, non-

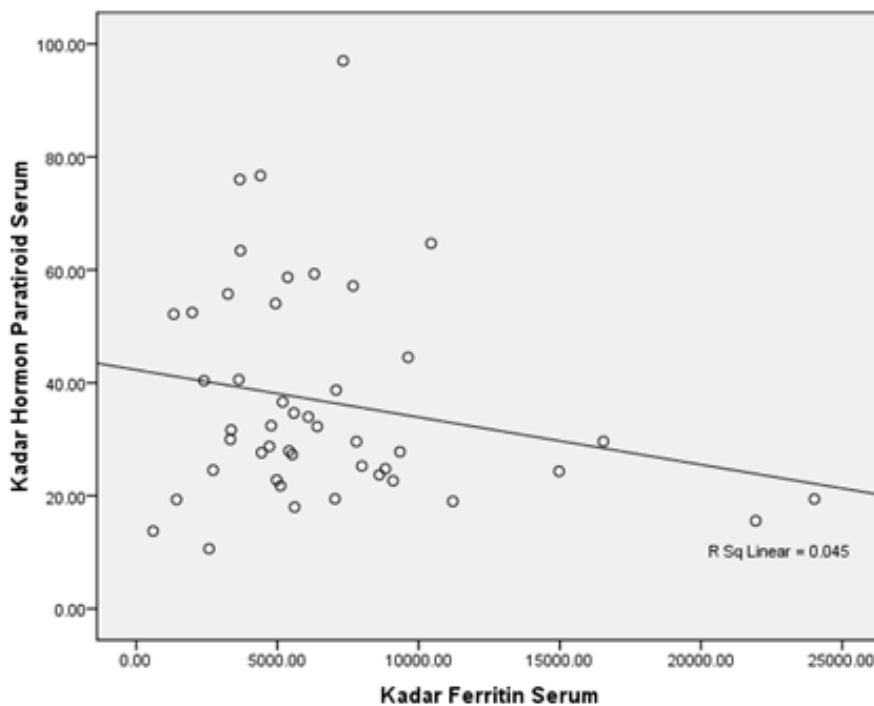
Table 1. Demographic and clinical characteristics of patients (n=46)

Characteristics	Frequency (%)	Median (IRQ)
Age (years)		25 (10)
Gender		
Male	26 (56.5)	
Female	20 (43.5)	
Duration of thalassemia (years)		7.5 (3)
Blood transfusion (unit/month)		2 (1)
Splenomegaly (Schaffner)		2 (0.25)
Clinical symptoms		
Fatigue	32 (62.7)	
Asthma	2 (3.9)	
Palpitations	6 (11.8)	
Fever	2 (3.9)	
Chest pain	2 (3.9)	
Bleeding	1 (2)	
Weight loss	7 (13.7)	
Chelation therapy		
Deferasirox	26 (56.5)	
deferiprone	20 (43.5)	
Non-adherence to iron chelation therapy	41 (89.1)	
History of diseases		
Cirrhosis	1 (2)	
Diabetes mellitus	1 (2)	
History of smoking	10 (19.6)	
History of alcohol consumption	1 (2)	
Blood screening		
Hb (g/dL)		6.8 (0.7)
MCV (fl), mean \pm SD		64.91 (6.72)
MCHC (g/dL)		31.65 (0.90)
WBC ($\times 10^3/\mu\text{L}$)		6.10 (2.72)
Neutrophil (%)		61.7 (10.1)
Lymphocytes (%)		31.6 (6.7)
Platelets ($\times 10^3/\mu\text{L}$)		277 (148)
SGOT (IU/L)		17 (3)
SGPT (IU/L)		19 (3)
BUN (mg/dL)		10 (4)
SCr (g/dL)		0.8 (0.2)

IQR: Interquartile range

Table 2. The distribution and the levels of patients' serum ferritin and parathyroid hormone ($n=46$)

Variables	Frequency	Median (IQR)	Range (min-max)
Serum ferritin (ng/mL)		5672.90 (4483.92)	596.80 – 24014.58
<1500	3		
1500-2500	2		
2500-5000	14		
5000-10000	21		
>10000	6		
Parathyroid hormone (pg/mL)		29.80 (28.74)	10.61 – 97.01
<15	2		
15-65	41		
>65	2		

**Figure 1.** Correlation between the levels of serum ferritin with parathyroid hormone in TDT patients.

adherence to such therapy was found in almost 90% of the patients. Laboratory investigation suggested that all the patients suffered from microcytic hypochromic anemia (mean hemoglobin (Hb): 6.8 mg/dL; mean corpuscular volume (MCV): 64.91 fL); mean corpuscular hemoglobin concentration (MCHC): 31.65 g/dL). The liver and renal functions were within normal limits.

Distributions and the levels of serum ferritin and parathyroid hormone among patients are presented in Table 2. The median level of serum ferritin was 5672.90 ng/mL (min-max: 596.80–24014.58 ng/mL), in which the highest distribution was found within the range of 5000–10000

ng/mL (21 patients). The median level of parathyroid hormone was 29.80 pg/mL (min-max: 10.61–97.01 pg/mL), with the highest distribution recorded within the range of 15–65 pg/mL.

The correlation of serum ferritin with parathyroid hormone is illustrated in Figure 1. Spearman correlation analysis suggested a negative correlation, but not statistically significant, between serum ferritin and parathyroid hormone ($r=-0.166$; $p=0.270$), indicating that the higher the level of serum ferritin, the lower the amount of parathyroid hormone in the plasma. We also identify the possible correlation of both serum ferritin and parathyroid hormone with age, duration

of thalassemia, and the number of transfusions, and the result revealed no significant association between all the tested variables ($p>0.05$), except between age and serum ferritin ($r=0.343$; $p=0.020$) (Table 3).

DISCUSSION

In the present study, we evaluated the correlation between the levels of serum ferritin with parathyroid hormone among adult TDT patients. Ferritin is an iron-binding protein consisting of 24 protein subunits surrounding an iron core. It is a storage form of iron, and its levels in the serum indicate iron status in the body.^{21,23,24} In this study, all the patients exhibited increased serum ferritin levels ranging from 596.80 – 24014.58 ng/mL (median: 5672.90 ng/mL) (Table 2), assumingly indicative of excess iron accumulation in the patients' body. This finding was in accordance with that reported previously, suggesting significantly higher serum ferritin levels in TDT patients as compared to healthy patients.²⁵

In TDT patients, iron overload occurs mainly as a result of repeated blood transfusion.^{21,24,26-29} This excess iron causes saturation of the circulating transferrin-binding iron, resulting in the formation of unstable iron called non-transferrin-binding iron (NTBI). These NTBI molecules are taken up by certain organs such as the liver, pancreas, myocardium, and endocrines to be accumulated as ferritin or hemosiderin.³⁰⁻³³ Once transferrin and ferritin become saturated, the level of NTBI increases, leading to the formation of reactive oxygen species (ROS) such as singlet oxygen, hydroxyl radical (OH), hydrogen peroxide (H₂O₂), and superoxide anion (O₂⁻).³⁰⁻³⁵ ROS

Table 3. The correlation of serum ferritin and parathyroid hormone with clinical characteristics of patients

Variables	Serum ferritin		Parathyroid hormone	
	R	p-value*	r	p-value*
Age	0.343	0.020	-0.042	0.780
Duration of thalassemia	-0.137	0.364	0.216	0.163
The number of transfusions (unit)	-0.056	0.722	-0.052	0.730

*Spearman correlation

causes oxidative damage to the affected organ through the induction of membrane lipid peroxidation and production of reactive and unstable peroxides.^{36,37} These peroxides lead to autocatalytic chain reaction propagation that results in damage to the mitochondrial, lysosomal, and sarcolemma membranes, as well as disruption of several transferrin receptors.³⁷ Rich anti-oxidant plants therefore are studied to prevent free-radicals associated health problems or diseases.³⁸

In terms of parathyroid hormone, we found a decreased parathyroid hormone secretion along with an increase of serum ferritin levels in the patients. The Spearman correlation suggested that serum ferritin was negatively correlated with parathyroid hormone in TDT patients, but the correlation was not statistically significant (Figure 1). This result was in accordance with those reported in a previous study, indicating that serum ferritin was inversely related to parathyroid hormone in TDT patients,^{25,39} in which the higher the serum ferritin levels, the lower the parathyroid hormone in the patients. These findings suggest a decreased parathyroid gland function in TDT patients, which was presumably associated with the presence of oxidative damage owing to excessive NTBI accumulation in this organ. Despite the exact mechanism of how iron overload causes damage to the tissue is not fully understood for parathyroid gland, excess iron has been reported to result in iron deposition in the thyroid gland. This iron deposition causes parenchymal fibrosis of the gland, leading to progressive dysfunction of the thyroid gland. The same mechanism of action has been assumed to also occur in the parathyroid glands.⁴⁰

We also examined the possible correlation of several demographic and clinical characteristics of the patients with serum ferritin levels and parathyroid hormone. We found that

age was significantly correlated with the level serum ferritin, in which serum ferritin increased along with aging. A possible explanation for this is that the patients might have started to develop asymptomatic inflammation associated with aging. A study reported that serum ferritin level can increase with aging as a part of an inflammaging state, an ongoing asymptomatic chronic systemic inflammatory state related to the aging process.^{41,42}

CONCLUSIONS

In the present study, TDT patients exhibited accelerated serum ferritin levels and decreased parathyroid hormone. Spearman correlation analysis suggested a negative correlation, but not statistically significant, between serum ferritin and parathyroid hormone in TDT patients, in which the higher serum ferritin levels, the lower the secretion of parathyroid hormone. Our finding suggests that the increment of plasma iron might lead to a decrease in parathyroid function. Thus, providing effective iron chelation in transfusion-dependent thalassemia patients, as well as increasing patients' adherence to iron chelation therapy is critical.

ETHICAL APPROVAL

Ethical approval was obtained from the Medical Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya. All patients provided signed informed consent prior to the study inclusion.

COMPETING INTERESTS

The authors declare no competing interest.

GRANT INFORMATION

None.

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