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The Relationship of Thyroid Hormone Levels (FT4-THSs) with Ferritin Levels in Thalassemia Patients

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Abstract : ***Introduction****: Thalassemia patients often experience anemia and require repeated transfusions. Repeated transfusions will result in a buildup of iron in the body which will cause dysfunction of the body's organs, including the thyroid gland. Ferritin is the major iron storage protein and is essential for iron homeostasis. This study aim to know the relationship between increased ferritin levels and thyroid hormone disorders in thalassemia patients.****Method****: A cross-sectional study conduct at Pediatric Departement, Wahidin Sudirohusodo Hospital in March - July 2023. Thalassemia patient who met inclusion criteria was measured ferritin, FT4, and TSHs level. The relationship between ferritin and thyroid hormone disorders was analyzed.* ***Results****: A total of 39 subjects. The mean age was 10,5 years. There was no relationship between FT4 and ferritin (p = 0,98). There was no relationship between TSHs and ferritin (p = 1,00), and there was no relationship between ferritin levels and thyroid hormone disorders in children with thalassemia (p = 0,94). The ferritin cut-off was 1154 ng/mL, but cannot be used as a reference for thyroid hormone disorders in thalassemia patients.****Conclusion****: There was no significant relationship between thyroid hormone levels and ferritin levels in children with thalassemia who underwent repeated transfusions.*

Keywords -*Children, Ferritin, FT4, Thalassemia,Thyroid hormone,TSHs*

I. Introduction

Thalassemia is a group of genetic disorders of globin chain production with an imbalance between the production of α-globin and β-globin chains. Thalassemia is the most common genetic disease in the world. It is estimated that every year around 100,000 children with thalassemia major are born worldwide. This genetic disease is caused by the inability of the bone marrow to form the protein needed to produce hemoglobin. Hemoglobin is an iron-rich protein found in red blood cells that functions to transport oxygen from the lungs to all parts of the body.[1,2]

In thalassemia there is a decrease in hemoglobin levels and lysis of erythrocytes which results in anemia and is the main problem in thalassemia, so thalassemia patients need repeated transfusions. This

repeated transfusions will result in a buildup of iron in the body which will result in dysfunction of the body's organs. Iron is toxic to the body, which tends to initiate redox reactions and produce free radicals and cause tissue damage. Iron must be controlled and stored in the body by binding to protein, in this case, ferritin. Ferritin is the major iron storage protein and is essential for iron homeostasis. Over time, excess iron causes the accumulation of excess iron in the body's organs, one of the main ones being the endocrine organs. One of the most important organs that experiences dysfunction is the thyroid. Dysfunction of the thyroid will result in thyroid hormone disruption, so that hypothyroidism can occur in thalassemia patients.[3-5]

The function of the thyroid gland is to produce thyroid hormones which have an important role in various metabolic processes in the body (protein, carbohydrate, and fat) and biological activities. In children, thyroid hormone deficiency has quite significant impacts, including mental disabilities, neurological disorders and the appearance of cretins. Cretin is a condition of mental retardation which can be accompanied by mutism, deafness, a distinctive way of standing and walking and stunted growth (short stature). Hypothyroidism is one of the most common side effects seen in patients with thalassemia. [6,7] Therefore the aim of this study is to determine the relationship between increased ferritin levels in thalassemia patients which can cause thyroid hormone disorders.

II. Methods

1.1 Study design and clinical setting

We conducted an observational study with a cross-sectional approach which aimed to analyze the relationship between hypothyroidism and ferritin levels in children with thalassemia. This research was conducted in the Pediatric Departement of Wahidin Sudirohusodo Hospital, Makassar in March - July 2023. Samples were taken using consecutive random sampling among beta thalassemia subjects aged 6 months to 18 years who underwent routine transfusions. This study was approved by the local ethics committee.

The inclusion criteria are (1) Children with beta thalassemia who undergo routine transfusions and are treated in one day care, inpatient or outpatient, at Wahidin Sudirohusodo Hospital; (2) Subjects aged 6 months to 18 years; (3) Patients and parents are willing to participate in this study. Meanwhile, the exclusion criteria are (1) Children with malignancy, malnutrition, infection and obesity; (2) children who suffer from thalassemia but do not receive blood transfusions. The patient's caregivers (parents) were given information and informed consent regarding participation and procedures in this study.

1.2 Measurement and outcome

Subjects who meet the criteria have their history recorded (name, age, gender, medical record number, body weight, nutritional status) and undergo laboratory examinations (Hb, ferritin, FT4, TSHs) and the results are documented. Laboratory examinations were carried out once by taking 3 ml of blood from a venipuncture. The samples that have been taken are then examined for serum ferritin levels and thyroid hormone function levels (FT4 and TSHs). After obtaining the results of the serum examination, the results were grouped by age and data analysis was carried out on the relationship between ferritin levels and thyroid hormone levels (FT4 and TSHs). The primary outcome measured in this study was the presence or absence of thyroid hormone secretion disorders as assessed through FT4 and TSHs examinations.

1.3 Data analysis

Data analysis used SPSS 24.0 software with univariate analysis and bivariate analysis. Univariate analysis was performed to describe patient baseline data. Meanwhile, bivariate analysis was conducting after data normality test with Shapiro Wilk. If the data is normally distributed ($p > 0.05$) then the student T-test is used, whereas if the data is not normally distributed then the Mann Whitney test is used. Data in the form of nominal data is carried out by the X2 (Chi-square) test. A p value <0.05 was considered statistically significant. We also performed a correlation test to determine the strength of the relationship between ferritin levels and thyroid disorders.

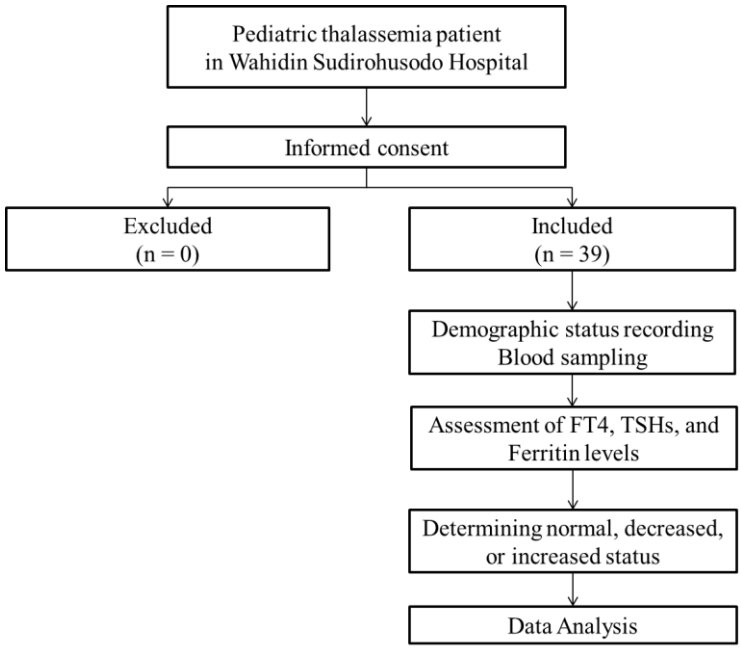

Fig. 1 Study flowchart.

III. Results

1.4 Characteristics of the research sample

During the study period, 39 patients met the inclusion criteria, consisting of 1 alpha thalassemia patient, 25 beta thalassemia patients and 13 HbE beta thalassemia patients. A total of 30 thalassemia patients had normal thyroid hormone levels and 9 thalassemia patients had disturbed thyroid hormone levels. There were no patients with undernutrition status among thalassemia patients in this study. wasting was found in 11 patients (84.6%) with thalassemia with normal thyroid hormone levels and 2 patients (15.4%) with thalassemia with disturbed thyroid hormone levels. There was one patient (100%) with alpha thalassemia with normal thyroid hormone levels. A total of 7 patients (28%) were diagnosed with beta thalassemia, and two patients diagnosed with HBE beta thalassemia had thyroid hormone disorders. A total of 3 patients (50%) with thalassemia had normal ferritin levels but disturbed thyroid hormone levels. Meanwhile, 6 patients (23.1%) with thalassemia had abnormal (high) ferritin levels accompanied by thyroid hormone disorders. In this study, there were no significant differences in demographic data and initial clinical data in participants with normal thyroid hormone vs. disturbed thyroid hormone. This data is presented in Table 1.

Table 1.Baseline characteristics of study participants.

Variable	Normal Thyroid Hormones n = 30 (76.9%)	AbnormalThyroidHormones n = 9 (23.1%)	P value
Gender			
Boy	13 (68.4%)	6 (31.6%)	0.219*
Girl	17 (85.0%)	3 (15.0%)	
Nutritional status			
Poor	0 (0%)	0 (0%)	
Wasted	11(84.6%)	2 (15.4%)	0.420*
Normal	19(73.1%)	7 (26.9%)	
Diagnosis			
Alpha	1 (100%)	0 (0%)	
Beta	18 (72%)	7 (38%)	0.584*
HBE	11 (84.6%)	2 (15.4%)	
Ferritin			
Low	1 (100%)	0 (0%)	
Normal	3 (50%)	3 (50%)	0.214*
High	26 (76.9%)	6 (23.1%)	
Age (years), median (SD)	10.50 (4.70)	10.00 (4.65)	0.885**
Hb (gr/dl), median (min-max)	7.55 (3.80-10.60)	8.70(5.90-11.60)	0.051**
MCV (fl), median (min-max)	71.50 (23.00-96.00)	72.00 (61.00-84.00)	0.731***
MCH (pg), median (min-max)	24.00 (13.00-74.00)	24.00 (20.00-30.00)	0.720***
RDW (fl), median (min-max)	24.5 (0.00-31.20)	22.80 (12.90-31.80)	0.858***

* Chi Square Test
** Independent t test
*** Mann Whitney Test

1.5 Differences in FT4 levels and Ferritin levels in thalassemia patients

There was 1 (100%) thalassemia patient who had normal FT4 levels and low ferritin levels. There was 1 patient (16.7%) with thalassemia who had low FT4 levels. At higher ferritin levels, there were 31 thalassemia patients (96.9%) with normal FT4 levels and 1 patient (3.1%) with disturbed FT4 levels. The results of the analysis test showed that there was no significant difference between FT4 levels and ferritin levels in thalassemia patients, with p value = 0.98 (p > 0.05). Data are presented in Table 2.

Table 2. Relationship between FT4 and Ferritin in Thalassemia Patients

Ferritin levels	FT4 levels		P value	OR value (95%CI)
	Normal	Abnormal		
Low	1 (100%)	0 (0%)		
Normal	5 (83.3%)	1 (16.7%)	0.98*	-
High	31 (96.9 %)	1 (3.1%)		

* Kolmogorov Smirnov test

1.6 Comparison of TSHs and Ferritin levels in thalassemia patients

In normal ferritin levels, there were 4 patients (66.7%) with normal TSHs levels and 2 patients (33.3%) with disturbed TSHs levels. Meanwhile, with higher ferritin levels, 26 patients (81.3%) had normal TSHs levels and 6 patients (18.8%) had disturbed TSH levels. The results of the analysis test showed that there was no significant difference between TSHs levels and ferritin levels in thalassemia patients, with a p value = 1.00 (p > 0.05).

Table 3. Relationship between TSHs and Ferritin in Thalassemia Patients

Ferritin levels	TSH levels		P value	OR value (95%CI)
	Normal	Abnormal		
Low	1 (100%)	0 (0%)		
Normal	4 (66.7%)	2 (33.3%)	1.00*	-
High	26 (81.3%)	6 (18.8%)		

* Kolmogorov Smirnov test

1.7 Comparison of thyroid hormone and ferritin in thalassemia patients

With normal ferritin levels, there were 3 patients (50%) with normal thyroid hormones and there were 3 patients (50%) with disturbed thyroid hormones. Meanwhile, with higher ferritin levels, 26 patients (76.9%) had normal thyroid levels and 6 patients (23.1%) had high thyroid hormone. The results of the statistical analysis test showed that there was no significant difference between thyroid hormone and ferritin levels in thalassemia patients, with p value = 0.94 ($p > 0.05$).

Table 4. Relationship between Thyroid Hormones and Ferritin in Thalassemia Patients

Ferritin	Thyroid Hormone		P value	OR value (95%CI)
	Normal	Abnormal		
Low	1 (100%)	0 (0%)		
Normal	3 (50%)	3 (50%)	0.94	-
High	26 (76.9%)	6 (23.1 %)		

* Kolmogorov Smirnov test

We determined the sensitivity and specificity cut-off points for ferritin levels to thyroid hormone levels using Youden index values and then calculated the accuracy of the various cut-off points. Comparative analysis of sensitivity, specificity, Positive Predictive Value (NPP) and Negative Predictive Value (NPN) at the cut point for thyroid hormone levels ≥ 1154.5200 ng/mL is depicted on the ROC curve.

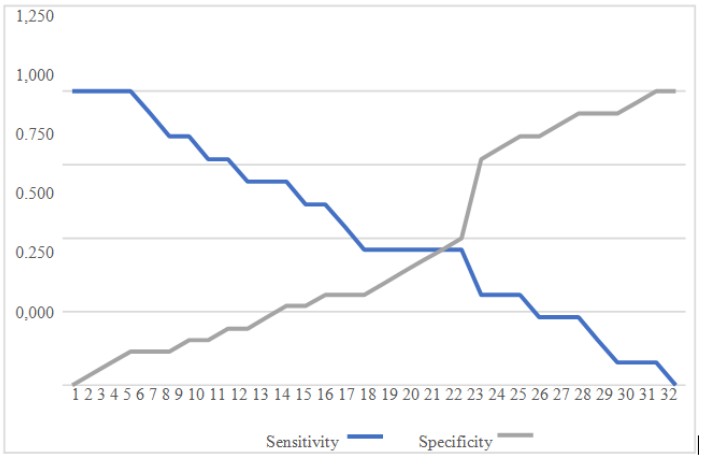

Fig. 2 Cut-off point curveof thyroid hormone levels in thalassemia children.

The ROC curve depicts sensitivity on the Y axis and specificity on the Y axis. Based on the ROC curve, a significant AUC value of 0.494 is obtained with a sensitivity of 46.15%, a specificity of 46.15%, a positive predictive value of 30.0% and a negative predictive value of 63.16%. This shows that in this study, Ferritin levels ≥ 1154.5200 ng/mL cannot be used as a reference for assessing the occurrence of thyroid hormone disorders in thalassemia children.

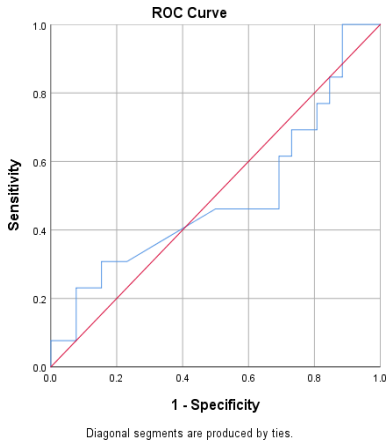

Fig. 3 Receiver Operating Characteristics(ROC) Ferritin specificity curve

IV. Discussion

Thalassemia is the most common single gene disorder. Disturbance in the formation of globin chains from the Hb molecule is a condition known as hemoglobinopathy.[8] This condition occurs in thalassemia patients and is inherited in an autosomal recessive manner. In this study, there were 39 samples with the mean age is 10 years, both in the normal thyroid hormone group and in the disturbed thyroid hormone group, this is similar with study by Kalimuddin Khan et al that there were no thalassemia patientsunder 10 year old in their study who has thyroid disorders. However, another study in India from 2013 to 2015 by Kavitha et al showed the occurrence of hypothyroidism or thyroid level disorders in thalassemia children even in the first decade of life.[9-10]

Thalassemia patients require regular blood transfusion therapy and iron chelation to maintain their quality of life. Patients must receive lifelong blood transfusions to treat anemia and maintain target HB levels > 10 gr/dl. Repeated transfusions will cause double the accumulation of iron. A paper published byFatqur Rahman stated that a transfusion of 9.5 – 10 units per year would cause a condition of hemosiderosis. A similar thing was also reported by Angel Remacha at the Virgen de la Salud Hospital in Spain, stating that repeated transfusions in children of more than 10 units/year would cause hemosiderosis.[11–13] High accumulation of iron in the body results in an increase in free iron which will stimulate the emergence of free reactive oxygen species (ROS). This occurs in cells where labile plasma iron is taken up and accumulated as stored iron (ferritin and hemosiderin). ROS result in lipid peroxidation, organelle and DNA damage as well as dysregulation of mechanisms involved in apoptotic cell death, which increases the risk of neoplasms such as hepatoma. Labile iron also becomes more available to microorganisms that bind to iron transferrin or ferritin, thereby increasing the risk of infection. These superoxide radicals oxidize cell membrane lipids and proteins as well as organelle membranes, causing cell damage and death.[14,15]

The process of iron deposition in the body occurs in important organs (especially the heart, liver and endocrine glands) which can result in tissue damage and organ dysfunction and failure. The endocrine gland that is often the site of iron deposition is the thyroid gland. Iron toxicity that occurs in the thyroid gland will result in disruption of the child's growth and development process. The cause of thyroid dysfunction in thalassemia patients is the accumulation of iron in the thyroid gland.[16–19]

This study consisted of 39 children suffering from thalassemia, some of whom had disturbed thyroid hormones. Similar withKalimuddin Khan et al that studied 80 thalassemia children, 9 (11.3%) children suffered from hypothyroidism and 71 (88.8%) children suffered from euthyroidism. This condition is in accordance with a study conducted in London by Grundy RG et al. In 18 thalassemia children who underwent transfusions, 11% of children experienced abnormal thyroid dysfunction. This also similiar with study by Ramadhan et al who reported that the majority of children with thalassemia did not have endocrine disorders.[10,20]

Endocrinopathy is a common condition found in thalassemia patients even though parenteral and oral iron chelation therapy has been given. This is because thalassemia patients experience long-term extravascular hemolysis, which increases iron absorption in the gastrointestinal tract or intestinal tract. This situation is combined with repeated blood transfusions, this situation causes iron overload and an increase in the amount of

iron in the tissue, which can cause progressive tissue damage in several organs including the thyroid gland and other organs which can trigger hydroxyl free radicals and oxidative stress in the tissue, causing organ failure or dysfunction. Other conditions such as hypogonadism are the most common endocrine problems in thalassemia patients which are mostly caused by repeated transfusions as well as organ siderosis, free radical damage and chronic tissue hypoxia. This condition can affect the secretion of FSH, LH and TRH, which is disrupted by the anterior pituitary gland experiencing dysfunction or damage.[10,21–24]

In our study, there were no significant differences between the ferritin levels of thalassemia patients with normal thyroid hormones and those with disturbed thyroid hormones. This condition is similiar with study by Burhan et al which stated that there were no significant results between ferritin levels in the euthyroid group and the hypothyroid group. There are several explanations for why significant relationships are not obtained. The most likely explanation is the polymorphism factor. Other studies have found that Thr92AlaD2 plays a role in hypothyroidism. Both of these things can cause hypothyroidism to occur in people with thalassemia with low ferritin levels or hypothyroidism does not occur even though high serum ferritin levels are found.[25]

In this study, there was also no relationship between TSHs levels and ferritin levels. These results are in line with the study by Solanki et al which reported that there was no correlation between serum TSHs and serum ferritin levels. A similar thing was also reported by Eshragi et al, they were not found correlation between TSHs and serum ferritin levels with a p value = 0.584 ($p > 0.05$). The results of another study were stated by Hassam et al, a negative correlation between serum TSHs and serum ferritin was found which was not statistically significant ($r=-0.014$, $P= 0.911$).[26]

In this study, there was also no relationship between FT4 levels and ferritin levels. These results are similiar with Zaghlol MS et al who explained that FT4 is not related and does not correlate with serum ferritin levels in children with thalassemia. The lack of association between ferritin and hypothyroidism can be explained by showing that endocrine gland damage caused by chronic hypoxia is more severe than that caused by hemosiderosis of the thyroid gland. The same condition was also described by Fayed HM et al, who found no significant differences between FT4 and ferritin in children with thalassemia. The same results were also described by Akinci et al, that there was no relationship between FT4 and ferritin in children with thalassemia.[10,27–29] Another condition that can support this study is explained in Kamil et al's research study which found no significant correlation between laboratory measurements of ferritin, TSHs fT4, fT3, FSH, LH, testosterone, and estradiol. Specifically, for fT4, a correlation coefficient of 0.39 and a p value of 0.13 are reported in the correlation analysis table. Therefore, there may be a weak relationship between ferritin and fT4, but the study of Kamil et al did not find a clear relationship between ferritin and fT4 parameters.[13,30-31]

However, all these results were different from the study by Kalimuddin et al. It was found that serum ferritin levels were significantly associated with serum FT4 levels (negative association) at a cut-off of more than 1414 ng/ml. There is a risk of developing hypothyroidism (low fT4) in subjects with high serum ferritin levels of more than 1414 ng/ml (T4 value, 005 with $p = 0.045$). There is a decrease in fT4 levels with increasing serum ferritin levels, very high serum ferritin levels when separated from relatively lower levels, become statistically significant.[10,32]

Determination of the cut-off point for ferritin levels for thyroid hormone was carried out in this study and the cut-off point was 1154 ng/mL, but this value cannot be used as a reference for assessing the presence of thyroid hormone disorders in thalassemia patients. Chirico et al in 2018 reported that the cut-off was 1800 ng/mL, while Gamberini et al in 2019 said a minimum of 3000 ng/m. These findings were supported by Adel et al in the same year who reported that the development of thyroid hormones was disrupted or hypothyroidism with a ferritin cut-off of 2000 ng/mL.[33]

The limitation of this study is that it cannot yet eliminate factors that can influence the results, which is the iron chelation status and the number of routine transfusions undertaken, where these criteria are not included in the factors studied in this study. Another limitation is the relatively small and unbalanced sample population between the alpha, beta major and beta HbE thalassemia groups.

V. Conclusion

There was no significant relationship between thyroid hormone levels and ferritin levels in children with thalassemia who underwent repeated transfusions. The cut-off value for ferritin levels in this study was 1154

ng/mL, but it cannot be used as a reference for thyroid hormone disorders in thalassemia patients. Suggestions for future research are to conduct research with a larger sample size with higher statistical power.

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