



# The Correlation Between Iron Overload and Endocrine Function in Adult Transfusion-Dependent Beta-Thalassemia Patients with Growth Retardation

Tubagus Djumhana Atmakusuma <sup>1</sup>  
Faizal Drissa Hasibuan<sup>2</sup>  
Dyah Purnamasari <sup>3</sup>

<sup>1</sup>Division of Hematology-Medical Oncology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital/Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia;

<sup>2</sup>Division of Hematology-Medical Oncology, Department of Internal Medicine, Yarsi Hospital, Jakarta, Indonesia; <sup>3</sup>Endocrine and Metabolic Division, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital/Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

**Background:** Iron overload is a major problem in patients with transfusion-dependent beta-thalassemia (TDT). Reports on the correlation between iron overload and endocrine function with growth retardation in such a population in Indonesia have not been established. Therefore, this study aims to obtain a profile of iron load and endocrine function of adult transfusion dependent beta-thalassemia patients and their correlation with growth retardation.

**Methods:** A cross-sectional study was performed, involving adult homozygous and HbE beta-thalassemia patients receiving blood transfusions at the Cipto Mangunkusumo Hospital, Jakarta. Iron overload was represented by serum ferritin (FS) and transferrin saturation (TS), while the endocrine function was examined by the Thyroid Stimulating Hormone-sensitive (TSHs), free T4 (fT4), and insulin-like growth factor-1 (IGF-1). The results were analyzed using bivariate analysis plus Pearson and Spearman correlation tests.

**Results:** In general, 58 subjects were selected from 224 adult transfusion dependent beta-thalassemia patients, consisting of 31 males (53.4%) and 27 females (46.6%). Furthermore, their median age was 21 (18–24) years, while the subclinical hypothyroid proportion was 32.7% and low IGF-1 levels were detected in 79.3% of the total population. There was a weak negative correlation between FS and fT4 (Spearman rho=−0.361; p=0.003), as well as IGF-1 (Spearman rho=−0.313; p=0.008), but FS and TSHs had no correlation (Spearman rho=0.074; p=0.29). Also, there was no correlation between ST with TSHs (Spearman rho=0.003; p=0.492), fT4 (Spearman rho=0.018; p=0.448), and IGF-1 (Spearman rho=−0.142; p=0.143).

**Conclusion:** Based on serum ferritin, iron overload is discovered to have a negative correlation with free T4 and insulin-like growth factor-1.

**Keywords:** IGF-1, TSHs, fT4, serum ferritin, transferrin saturation, transfusion-dependent thalassemia

Correspondence: Tubagus Djumhana Atmakusuma  
Division of Hematology-Medical Oncology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital/Faculty of Medicine Universitas Indonesia, Jalan Diponegoro No. 71, Jakarta Pusat, DKI Jakarta, Indonesia  
Tel +6221-3162497  
Email hom\_fkui@yahoo.com

## Background

Thalassemia is a hereditary disease caused by a defect in the synthesis of globin. Moreover, beta-thalassemia is the commonest type, affecting about 80–90 million people or 1.5% of the global population. Indonesia is one of the countries with a high thalassemia prevalence of the disease, where the beta-thalassemia trait carrier is estimated as about 3–10%.<sup>1,2</sup> With a population of approximately 250 million and a 20% birth rate, about 5000 babies are predicted to be born with beta-thalassemia.

Based on the data from Cipto Mangunkusumo Hospital (RSCM) in 2016, 9031 people were suffering from thalassemia major in Indonesia. Also, up to 441 adult patients (age over 18 years) were recorded in Kiara thalassemia and Hematology-oncology department of Internal Medicine clinics.<sup>3</sup>

Thalassemia major (TM) is one of the thalassemia phenotypes characterized by severe anemia. Patients with TM require regular red blood cell transfusions, which are mandatory for their survival, therefore this condition is called TDT. Repeated red blood cell transfusions lead to iron overload in tissues or organs, thereby causing an impairment called iron toxicity which has several targets including the endocrine system. In addition, endocrine disorders are often detected in those suffering from TDT. Some studies indicated approximately 40–50% of thalassemia patients that received adequate transfusion therapy remained to have endocrine disorders such as a decrease in hormone levels or substances produced by the endocrine organs.<sup>4–8</sup>

Many of the thalassemia patients in Cipto Mangunkusumo Hospital experience growth retardation which has an impact on their psychosocial development. Several factors contribute to the development of growth retardation such as inadequate transfusion causing chronic anemia, iron overload, malnutrition, and desferrioxamine toxicity. Iron overload in endocrine organs leads to hypogonadism, disorders of growth hormone-insulin-like growth factor 1 (GH-IGF-1) axis, and hypothyroidism.<sup>9–12</sup>

Iron toxicity is caused by an overload of the respective element, a condition related to non-transferrin-bound iron (NTBI). Furthermore, NTBI examination has not been standardized and is not available in Indonesia, but TS is used as a surrogate marker of this process.<sup>13–15</sup>

T2\* MRI is the gold standard for assessing iron overload and toxicity.<sup>16,17</sup> However, in centers with limited resources, serum ferritin (SF) is often used to assess iron overload. Besides, the pancreas is an endocrine organ routinely measured using MRI T2\*. The examination has become a standard procedure in developed countries, but it is still only used for study purposes in Indonesia. Since this sophisticated modality is not available nationwide, TS and SF are targeted to be used as surrogate markers of iron overload.

Soesanti et al<sup>18</sup> conducted a study on 67 children with thalassemia in 2012. The result showed the prevalence of endocrine disorders as follows: 64% growth retardation, 41% hypothyroidism, and 20% late puberty. There is no publication of endocrine function in adult TDT beta patients with growth retardation in Indonesia yet.

Therefore, this study aims to determine the correlation between iron overload and endocrine function.

## Methods

This was a cross-sectional study that obtained a profile of iron load and endocrine function correlation in adult beta TDT patients with growth retardation in Cipto Mangunkusumo Hospital in December 2017. The endocrine function was observed by the thyroid hormone levels (Thyroid Stimulating Hormone-sensitive/TSHs and free T4/FT4) and insulin-like growth factor-1 (IGF-1).

Patients diagnosed with beta-thalassemia and beta-HbE (with high-performance liquid chromatography/HPLC or microcapillary) aged 18 years with growth retardation were included as subjects. The exclusion criteria were HbsAg or anti-HCV positive patients or when the subject did not agree to participate. This study was approved by the Ethical Committee of the Faculty of Medicine, Universitas Indonesia, as listed on the Ethical Approval Letter number 1133/UN.2.F1/ETIK/2017. All patients provided appropriate informed consent and were treated in accordance with the Declaration of Helsinki.

The subjects were recruited consecutively from Kiara thalassemia Polyclinic and Hematology-oncology department of Internal Medicine clinic. Each of them passed through venous blood sampling prior to the transfusion process. The blood samples collected were up to two tubes, namely 7 mL and 3 mL in size. The TSHs, FT4, Ferritin, SF, and TS examinations were performed at the clinical pathology laboratory of Cipto Mangunkusumo Hospital Jakarta, using chemiluminescence immunoassay (CMIA) method by Abbott™ Architect® i1000/i2000 device. Levels of SI and TIBC were measured using the direct colorimetric method by Abbott™ Architect® c4000/8000 device. Meanwhile, IGF-1 level was measured using the Solid-Phase method Electro-Chemiluminescence Immunoassay (ECLIA) by Siemens™ Immulite® 1000.

The data obtained were analyzed using Pearson's correlation test for those with normal distribution or Spearman correlation test for the ones with an abnormal (non-parametric) distribution. Since data distribution was abnormal, the nonparametric Spearman correlation was used.

## Results

In December 2017, 68 people were diagnosed with growth retardation among 224 adult TDT beta patients in Kiara thalassemia Polyclinic and Hematology-oncology department of Internal Medicine clinic. Then, 10 of the 68 that

met the inclusion criteria were not willing to continue, therefore only 58 completed the study.

The subjects were 27 (46.6%) females and 31 (53.4%) males (Table 1). Furthermore, their median age was 21 years, with a range of 18 to 24 years. The number of homozygous beta-thalassemia patients was 31 (53.4%) and those with HbE beta-thalassemia were 27 (46.6%). The Mid Parental Height as a benchmark target for the patient's height was 161.25 cm. Meanwhile, the average height of the subjects was 149.05 cm.

## The Proportion of Endocrine Disorders on Study Subjects

Table 2 shows the proportion of low IGF-1 was 79.3%, and subclinical hypothyroidism was 32.7%. The subclinical hypothyroidism was characterized by elevated TSHs ( $\geq 5$  mu/L) with normal fT4 levels, and most patients had no complaints.

## The Correlation Between Iron Overload and Endocrine Function in Adult TDT Beta Patients

The results from Spearman's test showed no significant correlation between transferrin saturation with TSHs, fT4, and IGF-1 (Table 3).

**Table 1** Baseline Characteristics of Research Subject

Variables	N = 58
Gender, n (%)	
Male	31 (53.4)
Female	27 (46.6)
Diagnosis, n (%)	
Homozygous Beta Thalassemia	31 (53.4)
HbE Beta Thalassemia	27 (46.6)
Age (years), median (min-max)	21 (18–24)
Pre-transfusion hemoglobin, mean (SD)	8.98 (1.15)
Weight (kg), median (min-max)	40.9 (27–60)
BMI (kg/m <sup>2</sup> ), median (min-max)	18.79 (14.60–76.18)
Height (cm), mean (SD)	149.05 (8.47)
Mid Parental Height/MPH (cm), mean (SD)	161.25 (9.21)
Serum ferritin (ng/mL), median (min-max)	5,340 (355–22,352)
Transferrin saturation (%), median (min-max)	100 (9–107)
TSHs (mu/L), median (min-max)	3.36 (0.66–8.4)
fT4 (ng/dL), median (min-max)	1.11 (0.76–1.96)
IGF-I (ng/mL), median (min-max)	60.5 (24–206)
MRI T2 * Pancreas, median (min-max)	13.41 (3.96–57.4)

**Abbreviations:** SD, standard deviation; TSHs, thyroid stimulating hormone-sensitive; FT4, free T4; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging.

**Table 2** Proportion of Endocrine Function in Adult Beta TDT Patients with Growth Retardation

Variables	n (%)
Euthyroid or normal	39 (67.3)
Hypothyroidism	0
Subclinical hypothyroidism	19 (32.7)
IGF-I	
Normal	12 (20.7)
Low	46 (79.3)

**Abbreviations:** TDT, transfusion dependent thalassemia; IGF-1, insulin-like growth factor-1.

Meanwhile, there was a weak significant correlation between serum ferritin with fT4 and IGF-1 ( $r = -0.361$ ;  $p = 0.003$  and  $r = -0.313$ ;  $p = 0.008$ ), but FS and TSHs had no correlation (Table 4).

It can be concluded that there is a negative correlation between serum ferritin with fT4 and IGF-1. However, FS and TSHs have no correlation, hence transferrin saturation does not correlate with TSHs, fT4, and IGF-1.

## Discussion

This study is the first to report the proportion of endocrine function disorders in adult TDT patients with growth retardation and its correlation with iron overload in the Indonesian population, particularly in the RSCM Jakarta.

The average values of the subjects' TSHs and fT4 were in the normal range. But, there were 32.7% of patients with subclinical hypothyroidism, a condition that has an unclear mechanism in TDT beta occurrence. This is probably due to thyroid tissue damage causing iron overload which releases free radicals, while the pituitary has not been damaged. Low TSHs and fT4 levels were not detected, indicating there was no serious damage to the pituitary and thyroid glands due to iron overload.

In this study, the proportion of low IGF-1 was 79.3% with an average median value of 60.5 ng/mL. Poggi et al<sup>8</sup> did not report the proportion of low IGF-1, but only a mean value of

**Table 3** Correlation Between Transferrin Saturation with TSH, fT4 and IGF-1

Variables	R	P
Transferrin saturation-TSHs	0.003	0.492
Transferrin saturation-FT4	0.018	0.448
Transferrin saturation-IGF1	-0.142	0.143

**Abbreviations:** TSHs, thyroid stimulating hormone-sensitive; FT4, free T4; IGF-1, insulin-like growth factor-1.

**Table 4** The Correlation Between Serum Ferritin with TSH, fT4 and IGF-1

Variables	r	p
Serum ferritin-TSHs	0.074	0.290
Serum ferritin -fT4	-0.361	0.003*
Serum ferritin -IGF1	-0.313	0.008*

**Abbreviations:** TSHs, thyroid stimulating hormone-sensitive; fT4, free T4; IGF-1, insulin-like growth factor-I. **Note:** \*p<0.05.

88.2±39.9 ng/mL. However, Rashid et al<sup>20</sup> obtained 51.43%, and Soliman et al<sup>5</sup> obtained 67%. Also, Scacchi et al<sup>22</sup> reported 46.8% and Moayeri, and Oolomi<sup>25</sup> discovered 42% in the group that was growth retarded. From the description above, the proportion of low IGF-1 in this study was greater than in previous ones possibly due to the higher iron overload.

Iron overload on the pituitary, thyroid, and liver causes iron toxicity that damages the cells playing a role in the synthesis of TSH, fT4, and IGF-1. Consequently, the levels of these hormones are reduced, leading to hypothyroidism or growth retardation.

In the test conducted, transferrin saturation had no significant correlation with TSH, fT4, and IGF-1. Supposedly as a surrogate marker of iron overload, TS correlated with endocrine variables. This was probably because transferrin saturation measurements were performed only once. Hence, the effect of iron overload for a long time was not envisaged. Similarly, Al-Hakeim et al<sup>24</sup> reported there was no transferrin saturation correlation with TSH and T4.

There was a weak negative correlation between serum ferritin with fT4 and IGF-1 ( $r = -0.361$ ;  $p = 0.003$  and  $r = -0.313$ ;  $p = 0.008$ ), but serum ferritin and TSHs had no significant correlation ( $r = 0.074$ ;  $p = 0.29$ ). The correlation between FS with fT4 and IGF-1 showed a decreased fT4 and low IGF-1 due to iron overload in the thyroid gland and liver. In contrast to Soliman et al<sup>19</sup> there is no significant correlation between FS and IGF-1. This is related to Eshragi et al<sup>21</sup> that did not obtain any correlation between FS and hypothyroidism as well as Zervas et al<sup>23</sup> that obtained no correlation between FS and thyroid disorders. In other Soliman et al<sup>19</sup> studies, a negative correlation was obtained between FS and fT4, however, FS and TSH had no correlation, which is similar to this current study.

## Conclusions

In general, the proportion of IGF-1 is quite high, namely 79.3%, while that of subclinical hypothyroidism is 32.7% and MRI T2\* pancreas is 87.5% in the group of adult TDT

beta patients that experienced growth retardation. Proportions of with low value of in adult patients who experienced a beta TDT beta growth retardation. As assessed by serum ferritin, there is a negative correlation between iron overload with fT4 and IGF-1. However, there is no correlation between FS and TSHs, hence transferrin saturation does not correlate with TSHs, fT4, and IGF-1.

## Data Sharing Statement

Additional data can be requested by contacting the corresponding author on the email address provided.

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## Disclosure

The authors report no conflicts of interest in this work.

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