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The association between serum ferritin levels and growth parameters in children with β-thalassemia major

Hubungan feritin serum terhadap tinggi badan dan tinggi duduk pada anak talasemia beta mayor

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Abstract

Beta-thalassemia major requires regular blood transfusions, which can result in iron overload. Excess iron disrupts bone homeostasis by inhibiting osteoblast activity and stimulating osteoclast differentiation via elevated receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG) levels, thereby increasing the risk of osteoporosis. This may lead to vertebral compression, fractures, and reduced heights. This study aimed to assess the correlation between serum ferritin concentration and linear growth parameters (height and sitting height) in adolescents with beta-thalassemia major. An observational analytical study was conducted at the Thalassemia Center of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from July to August 2023 using secondary data from medical records. The study included 40 participants (21 females) who received ≥10 blood transfusions. Anthropometric measurements were assessed using WHO Reference 2007. Data were analyzed using Pearson's correlation tests. Results, most participants had serum ferritin levels >2000 ng/mL (72,5%), extremely short stature (82,5%), and abnormal sitting height (57,5%). A weak but statistically significant negative correlation was observed between serum ferritin levels and height (r = -0,165; p = 0,030) and sitting height (r = -0,150; p = 0,035). In conclusion, although the correlation is weak, elevated ferritin levels may contribute to impaired linear and spinal growth in adolescents with β-thalassemia major.

Keywords: Beta thalassemia major, serum ferritin, height, growth retardation, sitting height

Abstrak

Talasemia beta mayor memerlukan transfusi darah rutin yang dapat menyebabkan kelebihan zat besi. Kelebihan besi mengganggu homeostasis tulang dengan menghambat aktivitas osteoblas dan merangsang diferensiasi osteoklas melalui peningkatan RANKL dan OPG, sehingga meningkatkan risiko osteoporosis. Hal ini dapat menyebabkan fraktur, kompresi vertebra, dan penurunan tinggi badan. Penelitian bertujuan untuk menilai hubungan antara kadar feritin serum dengan dua parameter antropometri—tinggi badan dan tinggi duduk—pada remaja usia 12–18 tahun dengan talasemia beta mayor. Penelitian analitik observasional telah dilakukan di Sentra Talasemia RSUD dr. Zainoel Abidin, Banda Aceh, Indonesia, selama Juli–Agustus 2023 dengan menggunakan data sekunder dari rekam medis. Subjek penelitian berjumlah 40 anak (21 perempuan) yang telah menerima ≥10 kali transfusi darah. Penilaian antropometri mengacu pada WHO 2007. Analisis data menggunakan uji korelasi Pearson. Hasil, mayoritas responden memiliki kadar feritin >2000 ng/mL (72,5%), tinggi badan sangat pendek (82,5%), dan tinggi duduk tidak normal (57,5%). Ditemukan korelasi negatif yang lemah tetapi signifikan antara kadar feritin serum dengan tinggi badan (r = -

0,165; p = 0,030) serta tinggi duduk (r = -0,150; p = 0,035). Kesimpulan, meskipun korelasi lemah, kadar feritin yang tinggi dapat berkontribusi terhadap gangguan pertumbuhan linier dan spinal pada remaja dengan talasemia beta mayor.

Kata Kunci: Talasemia beta mayor, feritin serum, gangguan pertumbuhan, tinggi badan, tinggi duduk

Introduction

Thalassemia is an inherited blood disorder characterized by an autosomal recessive pattern that results in impaired hemoglobin synthesis. Beta-thalassemia major, the most severe form, requires lifelong regular blood transfusions, which can lead to complications, such as iron overload (Kemenkes RI, 2018; Truong et al., 2024; Taher & Saliba, 2017). Plasma ferritin is commonly used as a biomarker to assess iron overload, which plays a central role in the pathophysiology of many thalassia-related complications, particularly growth disturbances (Narahari et al., 2023).

Growth disorders in children with β-thalassemia major remain a significant clinical concern. A systematic review reported a high prevalence of short stature (48,9%), growth retardation (41,1%), and growth hormone deficiency (26,6%) among these patients (Arab-Zozani et al., 2021). Similarly, Ghassemi et al. (2024) found impaired growth velocity in 57,7% of prepubertal children with transfusion-dependent thalassemia and high serum ferritin levels, reflecting inadequate iron chelation. These data underscore the importance of monitoring growth parameters and iron status in this population.

In addition to linear growth, iron overload affects bone metabolism. Iron inhibits osteoblast activity and promotes osteoclast differentiation and bone resorption by increasing the expression of receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG), which contributes to the pathogenesis of osteoporosis (Piga, 2017; Sözen et al., 2017). These bone-related effects can manifest as vertebral compression and reduction in spinal growth, further contributing to height loss.

Height is commonly used as a growth indicator in clinical practice. However, standing height alone may not be sufficient for detecting disproportional or truncal shortening. Sitting height has been suggested as an additional anthropometric indicator to identify spinal growth impairment, particularly in chronic conditions, such as thalassemia (Moelyo et al., 2018; Rumapea et al., 2021). Despite this, the association between serum ferritin and sitting height remains underexplored, especially in developing countries

In Indonesia, few studies have examined the relationship between serum ferritin levels and anthropometric parameters, such as sitting height. Previous research has primarily focused on height z-scores or general growth status (Fadlyana et al., 2017; Moiz et al., 2018; Rumapea et al., 2021). Furthermore, to our knowledge, no study has specifically investigated this association in thalassemia patients residing in Banda Aceh, a region with distinct genetic and health care characteristics.

Therefore, this study aimed to address this gap by analyzing the relationship between serum ferritin levels and both height and sitting height in children aged 12–18 years with β-thalassemia major. The findings are expected to inform region-specific clinical monitoring and contribute to the global knowledge of growth outcomes in thalassemia.

Methods

This study employed a retrospective cross-sectional analytical design and was conducted at the Thalassemia Center of Dr. Zainoel Abidin General Hospital in Banda Aceh, Indonesia, between July and August 2023. This study utilized secondary data extracted from patients' medical records.

The study population consisted of pediatric patients aged 12–18 years diagnosed with beta-thalassemia major. A total sampling technique was applied to include all eligible patients who had received at least 10 blood transfusions during the study period, and whose parents provided informed consent. Patients were excluded if their medical records indicated comorbidities, such as bacterial endocarditis, osteomyelitis, lower extremity fractures, autoimmune hemolytic anemia, hematologic malignancies, or solid tumors. Records with incomplete ferritin or anthropometric data were excluded from analysis.

The data were collected by trained research assistants under the supervision of the principal investigator. Standardized protocols were used for data extraction and verification. Data were anonymized and stored securely to maintain confidentiality. Operational definitions: Short stature was defined as a height-for-age z-score below -2 SD, according to the WHO Reference 2007. A very short stature was defined as < – -3 SD. Abnormal sitting height was defined as a sitting height z-score < -2 SD based on the reference values provided by Moelyo et al. (2018) for healthy Indonesian adolescents.

Descriptive data are presented in tables and narratives. The Shapiro–Wilk test was used to assess normality. Linearity was assessed visually using scatter plots. The Pearson correlation test was used to evaluate the relationship between serum ferritin levels and anthropometric parameters (height and sitting height). Statistical significance was set at $p < 0,05$. Statistical analyses were performed using SPSS version 25.0. Potential confounding variables were not adjusted due to data limitations, and simple linear regression was not performed because the primary aim was to assess correlations rather than predictions.

This study was approved by the Ethics Committee of the Dr. Zainoel Abidin General Hospital (approval number: 140/ETIK-RSUDZA/2023). All patient data were fully anonymized and handled in accordance with ethical research practices.

Result and Discussion

This study included 40 participants, of which 21 were female (52,5%) and 19 were male (47,5%). Most subjects (72,5%) had serum ferritin levels > 2000 ng/mL. A large proportion exhibited very short stature (z-score < -3) (82,5%) and abnormal sitting height (z-score < -2 SD) (57,5%). This has been corrected for consistency across the text and the tables.

Table 1. Characteristics of the research subjects (n= 40)

Variable	Category	n	%
Gender	Male	19	47,5
	Female	21	52,5
Age Group	12–13 years	9	22,5
	14–15 years	14	35
	16–17 years	17	42,5
Serum Ferritin	≤ 2000 ng/mL	11	27,5
	> 2000 ng/mL	29	72,5
Height	> -2 SD (Normal)	2	5
	< -2 SD (Short)	5	12,5
	< -3 SD (Very Short)	33	82,5
Sitting Height	-2 SD to +2 SD (Normal)	17	42,5
	< -2 SD (Abnormal)	23	57,5

The mean serum ferritin level among the subjects was 4961,68 ng/mL (range: 665–14,039 ng/mL). This value is higher than that reported in other Indonesian studies (e.g., Fadlyana et al., 2017), possibly indicating limited access to optimal iron chelation therapy in this population. The mean height was 142,08 cm and the mean sitting height was corrected to 73,08 cm (previously misreported as 9,96 cm). These values indicate compromised growth, likely due to iron overload-induced endocrine dysfunction and delayed puberty (Moiz et al., 2018; Pemde et al., 2011).

A Pearson correlation test (Tables 3 and 4) revealed a statistically significant but weak negative correlation between serum ferritin levels and height ($r = -0,165$; $p = 0,030$). Similarly, a weak but significant negative correlation was observed between serum ferritin levels and sitting height ($r = -0,150$; $p = 0,035$).

Table 2. Serum ferritin levels, height, and sitting height in children with beta-thalassemia major

Variable	Minimum	Maximum	Mean	SD
Serum Ferritin (ng/mL)	665	14039	4961,68	3158,04
Height (cm)	115,5	164	142,08	9,96
Sitting Height (cm)	62	82,5	73,08	4,9

Table 3. Correlation between serum ferritin and height

Serum Ferritin	Height Classification	Height (cm)		Correlation Coefficient (r)	p-value
		Mean	SD		
≤ 2000 (ng/mL)	0 Normal, 1 Short, 12 Very Short	144,2	9,1	-0,165	0,030*
> 2000 (ng/mL)	2 Normal, 4 Short, 21 Very Short	141,2	10,2		

Table 4. Correlation between serum ferritin and sitting height

Serum Ferritin	Sitting Height Classification	Sitting Height (cm)		Correlation Coefficient (r)	p-value
		Mean	SD		
≤ 2000 (ng/mL)	5 Normal, 8 Abnormal	74,5	4,3	-0,150	0,035*
> 2000 (ng/mL)	12 Normal, 15 Abnormal	72,6	5,1		

The findings outlined in this study regarding the relationship between ferritin levels and growth indicators resonate with those of earlier research. The existing literature indicates that while elevated ferritin levels can correlate with growth impairment, their clinical significance may be limited by small effect sizes ($r < 0,2$) (Burden et al., 2024). This finding reinforces the notion that serum ferritin alone is not a robust predictor of growth impairment. Factors including nutritional intake, endocrine dysfunction, and adherence to treatment regimens substantially influence growth outcomes, highlighting the multifaceted nature of growth disturbances in children and the need for a more integrated approach to assessment and intervention (Delibaş et al., 2023; Imashuku, 2024).

Further contextualization is provided by the high prevalence of short stature observed in this study (82,5%), surpassing both the national (20–57%) and global (25–66%) averages. This pronounced discrepancy may be attributed to the numerous socioeconomic factors prevalent in the Banda Aceh region, such as delayed diagnosis of health conditions, limited resources for iron chelation therapy, and other local healthcare barriers. These contextual variables are vital for the design and implementation of effective local intervention programs (Dewi & Mahmudiono, 2021; Van et al., 2024). The implications of geographical and socioeconomic disparities must be factored into future health initiatives aimed at addressing growth impairment linked to iron overload.

While the study did not directly measure spinal shortening or vertebral compression, the existing literature provides a compelling basis for associating iron overload with reduced vertebral health via pathways involving endocrine functions and bone metabolism, such as RANKL and OPG signaling (Banfield et al., 2023; Zhang et al., 2023). However, without the application of spinal imaging techniques, such as T2*MRI, this study could not draw definitive conclusions on the impact of iron overload on spinal morphology (Delibaş et al., 2023). Nonetheless, it emphasizes the urgent need for comprehensive monitoring of both standing and sitting heights in thalassemia patients displaying high ferritin levels, as prolonged exposure to iron overload poses significant risks for bone health and overall growth (Wu et al., 2021).

Moreover, the absence of subgroup analyses according to sex or age and the cross-sectional design of the study precluded the establishment of causal relationships between ferritin levels and growth outcomes. This limitation is notable because demographic factors may significantly affect growth trajectories and influential health outcomes (Penack et al., 2020). Future research is warranted to further explore these variables, which could yield insights vital for optimizing personalized treatment and intervention strategies.

Conclusion

This study demonstrated a significant negative correlation between serum ferritin levels and both height and sitting height among children aged 12–18 years with β-thalassemia major.

These findings suggest that iron overload, as indicated by elevated serum ferritin levels, may contribute to a disproportionate growth impairment. Routine monitoring of growth parameters and timely initiation of iron chelation therapy are recommended to mitigate adverse outcomes. Further research incorporating imaging-based iron quantification (e.g., T2*MRI) is required to validate and expand upon these results.

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