Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6, 9230-9235
2024
Publisher: Learning Gate
DOI: 10.55214/25768484.v8i6.3978

Correlation between ferritin levels and lipid profile in children with transfusion-dependent thalassemia at Dr Soetomo general hospital, surabaya

Rivans Jackson Tandirerung[1], Andi Cahyadi[2], Mia Ratwita Andarsini[3*], Nur Aisiyah Widjaja[4]
[1,2,3,4]Department of Child Health, Faculty of Medicine Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia; drrivanstandirerung@gmail.com (R.J.T.) andimblitar@yahoo.com (A.C.) mia-r-a@fk.unair.ac.id (M.R.A.) nuril08@yahoo.com (N.A.W.)

Abstract: High levels of ferritin and adherence to low iron chelation are associated with the incidence of dyslipidemia. This process potentially causes some harmful effects, such as atherosclerosis. However, the correlation between ferritin level and lipid profile in thalassemia is still widely varied. The aim of this research was conducted to study the relationship between ferritin level and lipid profile. This research was a cross-sectional study involving 35 patients aged 5-18 years, diagnosed with transfusion-dependent thalassemia at Dr Soetomo General Hospital, Surabaya, Indonesia in November 2022. The sample was chosen by a consecutive non-randomized sampling technique. Patients previously diagnosed with dyslipidemia, diabetes mellitus type 1 and 2, metabolic syndrome, and having a history of anti-dyslipidemia medication and corticosteroids were excluded. Data were obtained from the medical record. Subsequently, the blood sample was drawn before the patients received any blood transfusion and examined for ferritin, total cholesterol, LDL, HDL, Triglyceride, apoA, and apoB levels. The data was analysed descriptively and the correlation between ferritin level and lipid profile was analysed statistically using Spearman, Pearson, and Chi-Square. According to the statistical analysis, a significant correlation was found between ferritin and LDL level ($p = 0.013$; coefficient correlation = 0.414), and total cholesterol ($p = 0.006$; coefficient correlation = 0.457). Meanwhile, ferritin level was not significantly related to high-density lipoprotein ($p = 0.283$), triglyceride ($p = 0.131$), apolipoprotein A ($p = 0.83$), apolipoprotein B ($p = 0.26$). Ferritin level was correlated significantly to LDL and total cholesterol level.

Keywords: *Dyslipidemia, Indonesia, Iron, Paediatrics.*

1. Introduction

High levels of ferritin and adherence to low iron chelation are associated with the incidence of dyslipidemia.[1] Dyslipidemia in thalassemia is possibly caused by increased erythropoiesis which accelerates cholesterol absorption by macrophages and histiocytes in the reticuloendothelial system, as well as liver damage due to liver iron overload, activation of the macrophage system with the release of cytokines, and hormonal disturbances.[2,3,4,5] Moreover, lipid levels, especially cholesterol, are regulated by the liver so that excess iron that accumulates in the liver will interfere with lipid synthesis. Dyslipidemia has been shown to play a role in the harmful effects of excess fat levels since high cholesterol, low High-Density Lipoprotein (HDL), and high Low-Density Lipoprotein (LDL) are associated with atherosclerosis.[6]

Although the correlation between dyslipidemia and high ferritin was reported, it is still controversial as the results of lipid profiles in patients with thalassemia widely varied according to several studies in different countries.[7,8,9,10] Therefore, this research was conducted to study the relationship between ferritin level and lipid profile to provide data for further research.

* Correspondence: mia-r-a@fk.unair.ac.id

2. Materials and Methods

This research was a cross-sectional study involving 35 pediatric patients with transfusion-dependent thalassemia at Dr Soetomo General Hospital, Surabaya, Indonesia in November 2022. The inclusion criteria were children 5-18 years old with transfusion-dependent thalassemia. The exclusion criteria included patients previously diagnosed with dyslipidemia, diabetes mellitus type 1 and 2, metabolic syndrome, and having a history of anti-dyslipidemia medication and corticosteroids. The sample was chosen by a consecutive non-randomized sampling technique. The independent variable was ferritin level, while the dependent variables were the levels of total cholesterol, LDL, HDL, Triglyceride, Apolipoprotein A (apoA) and Apolipoprotein B (apoB).

Subjects were initially assessed if they met the inclusion and exclusions criteria, subsequently listed and asked for informed consent. Demographic data, age, age of diagnosis and first transfusion were obtained from the medical record. Body Mass Index (BMI) was calculated according to the anthropometry measurement. Subsequently, the blood sample was drawn before the patients received any blood transfusion and examined for ferritin, total cholesterol, LDL, HDL, Triglyceride, apoA, and apoB levels.

Statistic analysis was done using SPSS version 16.0 afterwards. The characteristic of the subjects was analysed descriptively. The correlation of numerical data was assessed using Pearson correlation if the data is normally distributed and Spearman correlation if the data is not normally distributed. Meanwhile, the correlation of categorical data was assessed using chi-square.

3. Results

The descriptive statistic analysis was provided in detail in Table 1 and Table 2.

Table 1.
The characteristic of subjects.

Characteristic	f	%
Sex		
Male	17	48.6
Female	18	51.4
Age		
Child (<10 years old)	6	17.1
Adolescent (>10 years old)	29	82.9
Age when first diagnosed		
Infant (<1 year old)	2	5.7
Child (>1 year old)	33	94.3
Age when first transfused		
Infant	2	5.7
Child	33	94.3
BMI		
Underweight	9	25.7
Healthy weight	25	71.4
Overweight	0	0
Obesity	1	2.9

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 9230-9235, 2024
DOI: 10.55214/25768484.v8i6.3978

Abbreviations: f, frequency; BMI, Body Mass Index; %, percentage

Table 2.
Mean/median of the subject characteristic.

Characteristic	Mean	Median	Min.	Max.	Unit
Total cholesterol	103.171 ± 23.17				mg/dL
LDL	40.54 ± 19.32				mg/dL
HDL	25.8 ± 5.28				mg/dL
Triglyceride*	184.14 ± 66.24	162	94	345	mg/dL
ApoA	100.25 ± 13.03				mg/dL
ApoB	57.330 ± 14.29				mg/dL

Notes: *the Kolmogorov-Smirnov Significance value is less than 0.05, showing that the data is not normally distributed. Thus, the median, minimum, and maximum values are provided in the table.

Abbreviations: LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; ApoA, Apolipoprotein A; ApoB, Apolipoprotein B.

Based on the correlation study, a significant correlation was found between ferritin and LDL level ($p = 0.013$; coefficient correlation = 0.414), and total cholesterol ($p = 0.006$; coefficient correlation = 0.457). Meanwhile, ferritin level was not significantly related to HDL ($p = 0.283$), triglyceride ($p = 0.131$), apoA ($p = 0.83$), apoB ($p = 0.26$)

4. Discussion

Patients with thalassemia generally have higher iron serum level due to regular blood transfusions, massive hemolysis, or higher iron intake. The increase of iron serum level can be greater with inadequate iron chelating medication. The high iron serum level is associated with the incidence of many comorbidities, including dyslipidemia. The comorbidities caused by dyslipidemia are worsened by stress oxidative due to iron overload, causing susceptibility to atherosclerosis and its complications.[11]

This study resulted in a higher number of female subjects in this study (51.4%). A study in Korea showed that the number of females diagnosed with thalassemia was consistently higher than males as well. This might be affected by the fact that females are more sensitive to the symptoms of anaemia compared to males.[12]

In this study, the nutritional status of children with transfusion-dependent thalassemia is assessed using the BMI value. The BMI has an average value of 16.53 (SD ± 2.53) and 25% of the subjects had underweight status. This result was similar to the results of the study by Jabbar et al. (2022), showing that BMI in patients with thalassemia was transfusion dependent 16.10 (SE ± 0.26).[13] Patients with thalassemia have a higher risk of experiencing nutritional deficiencies due to increased of demand and inadequate absorption of nutrients. [14,15] This fact is supported by a study stating that supplement has weak effect in improving nutrition. Instead, iron overload has bigger impacts in vitamins and minerals deficiency.[16] Iron overload also causes endocrine dysfunction, leading to lacking growth hormones.[14] In addition, nutritional status in pediatric thalassemia is potentially influenced by multiple factors, including age, sex, and ethnicity. Therefore, further studies are needed to determine the significance of each contributing factor while excluding the disturbing factors.[17]

The high ferritin serum level in this study is in accordance with research by Betts et al in 2020, stating that the average serum ferritin in patients with transfusion-dependent thalassemia is more than 1000ng/ml. High ferritin serum indicates that these patients have a high risk of organ damage.[18] Ferritin serum levels are influenced by many factors, such as age, age when first transfused, age when first received chelation therapy, the efficacy of iron chelation drugs, and patient adherence to treatment.[19]

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 9230-9235, 2024
DOI: 10.55214/25768484.v8i6.3978

In this study, dyslipidemia occurred in all patients. A nationwide population study in Korea found that dyslipidemia occurred in 16% of thalassemia patients having a history of receiving blood transfusions. Dyslipidemia is related to blood transfusion as the occurrence is higher compared to transfusion-naive thalassemia (10%).[12] This finding supports the result of this research that all the patients had dyslipidemia since the subjects were transfusion-dependent thalassemia

The lipid profile has been shown to be significantly lower in patients with β thalassemia major.[20] This is possibly caused by plasma dilution due to anaemia, accelerated erythropoiesis resulting in increased absorption of cholesterol by macrophages, impaired liver function, hormonal disturbances, and low activity of hepatic and extrahepatic lipase enzymes, and rapid clearance of modified HDL and LDL by activated monocytes and macrophages. In addition, lipid abnormalities can also be caused by excessive iron loading, causing a high average serum ferritin level.[21] Low total cholesterol levels play a role in efforts to protect the body of patients with β thalassemia major in preventing Cardio-Vascular Disease (CVD) due to oxidative stress.[20]

This study shows that there was a significant relationship between ferritin levels and total cholesterol levels (p=0.013). This is in accordance with the study by Sengsuk et al., (p=0.07) yet different from research conducted by Jabbar et al., (p=0.6563).[13,20] Low total cholesterol level in thalassemia is possibly caused by erithropoietic hyperactivity requiring higher demand of cholesterol. Besides, excessive iron in blood may injure the liver, causing decrese in cholesterol secreted by the liver. However, some mechanism also explains increase of cholesterol serum level in thalassemia, which is decrease in cholesterol uptake by liver, leading to higher circulating cholesterol in blood.[11]

Based on this study, there was a significant positive relationship between ferritin levels and LDL cholesterol levels (p=0.013). This result is still controversial as it is in line with research by Suman et al., in 2017 (p=0.001), but in contrast to the study held by Jabbar et al., in 2022 (p=0.655).[1,13] High LDL uptake by histiocytes and macrophages causes the low level of LDL in thalassemia.[11] The low LDL levels play a role in protecting the patients from CVD due to oxidative stress.[20] In contrast, high LDL in thalassemia is possible as high iron level causes LDL to increase, explaining the positive correlation of ferritin and LDL in this study. Besides, iron chelating agent was proven to be effective in controlling ferritin as well as LDL level.[11]

According to the analysis, there was no significant relationship between ferritin levels and HDL cholesterol levels (p=0.283). These results are in line with research by Jabbar et al. in 2022 (p=0.819).[13] However, it is in contrast to another study (p <0.001).[20] HDL cholesterol levels were found to be significantly lower in patients with β thalassemia major. However, a study found the role of iron chelating agent in increasing the HDL and play a role in protection against oxidative stress and LDL cholesterol oxidation.[11,20,21] Those conditions explains the controversial relationship between ferritin and LDL among studies.

This research found a significant correlation between ferritin levels and triglyceride levels (p=0.006). These results are in line with research by Jabbar et al. (p=0.031) yet not in accordance with another study (p=0.109).[13,22] The high TG levels in thalassemia is caused by extrahepatic lipolytic hypoactivity.[11]

There was no significant relationship between ferritin and apolipoprotein A levels in this research (p=0.83). These results are not in line with previous studies by Al-Quobaili et al. in 2004 resulting in a significant relationship between ferritin and apolipoprotein A levels. As the serum ferritin level increased, lipoprotein A levels decreased.[3] This was supported by Sengsuk's research about high serum ferritin shows high levels of iron in the blood, causing oxidative stress and damage to the liver significantly, and affecting the reduction of apoA.[20] In addition, research conducted by Papanastasiou et al., in 1996 showed that there is a relationship between ferritin and apoA levels. This is due to many factors affecting iron levels in the blood, hormonal disturbances, damage to the liver and aging that affect fat and lipoprotein metabolism.[4] However, research conducted by Kamal and Talal showed that the lipid profile in thalassemia patients was not affected by iron levels, liver disorders, and age except due to erythroid bone activity with cholesterol consumption being more responsible for the results obtained.[23]

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 9230-9235, 2024
DOI: 10.55214/25768484.v8i6.3978

According to this study, ferritin was not significantly correlated to apolipoprotein B levels in transfusion-dependent thalassemia patients (p=0.26). Studies conducted by Al-Quobaili et al. in 2004 and Papanastasiou et al. in 1996 found a significant relationship between serum ferritin in thalassemia.[3,4] The same mechanism occurs at the concentration of apolipoprotein B with apolipoprotein A. Research conducted by Sengsuk et al. in 2014 shows that oxidative stress can damage the liver causing poor fat metabolism and increasing apolipoprotein B and LDL levels.[20]

5. Conclusion

Ferritin level was significantly correlated to LDL and total cholesterol levels. Oppositely, there was no significant relationship between ferritin levels and HDL, triglyceride, apoA, and apoB levels.

Acknowledgments:

We would like to express our gratitude to teaching staffs, outpatient clinic staffs, and residents at Department of Child Health, Dr Soetomo General Hospital, Surabaya, Indonesia.

References

[1] Suman R, Sanadhya A, Meena P, et al, "Lipid profile in children of β-thalassemia mayor and their correlation with serum ferritin," *Int J Contemp Pediatr*, pp. 543–547, 2017.

[2] Shalev H, Kapelushnik J, Moser A, et al, "Hypocholesterolemia in chronic anemias with increased erythropoietic activity," *Am J Hematol*, pp. 199-202, 2007.

[3] Al-Quobaili FA, Abou Asali IE. "Serum levels of lipids and lipoproteins in Syrian patients with beta-thalassemia major," *Saudi Med J.*, pp. 871-875, 2004.

[4] Papanastasiou DA, Siorokou T, Haliotis FA. "Beta-thalassaemia and factors affecting the metabolism of lipids and lipoproteins." *Haematologia.*, pp. 143-53, 1996.

[5] Deiana L, Garuti R, Pes GM, et al. "Influence of beta-thalassemia on the phenotypic expression of heterozygous familial hypercholesterolemia: a study of patients with familial hypercholesterolemia from Sardinia." *Arterioscler Thromb Vasc Biol.*, pp. 235-43, 2000.

[6] Mansi M and Aburjal TA. "Lipid profile in Jordanian children with β-thalassemia mayor." *Int J Hematol Oncol.*, pp. 93-8, 2008.

[7] Ashar S, Sultan S, Irfan SM, and Sheeraz A. "Serum fasting lipid profile in children and adolescents with β-thalassemia mayor in Southern Pakistan." *Malaysian J Pathol.*, pp. 233-238, 2015.

[8] Hendarto A, Sari TT, Rahmartani LD, Widyasari A and Iskandar SD. "Glucose and lipid profile in adolescents with thalassemia major and its association with iron overload in specific organs." *Indones Biomed J.*, pp. 188-193, 2019.

[9] Bordbar M, Haghpanah S, Afrasiabi A, Dehbozorgian J, and Karimi M. "Genotype-phenotype correlation related to lipid profile in beta-thalassemia major and intermedia in southern Iran." *J Clin Lipido*, pp. 108-113, 2012.

[10] Haghpanah S, Davani M, Samadi B, Ashrafi A, and Karimi M., "Serum lipid profiles in patients with beta-thalassemia major and intermedia in Southern Iran." *J Res Med Sci*, pp. 150-154, 2010.

[11] Sayed SZ, Maher SE, Adel G, et al., "Lipid profile in children with b-thalassemia major." *Egyptian Journal of Haematology*, pp. 183-186, 2012.

[12] Lee JS, Rhee TM, Jeon K, et al., "Epidemiologic Trends of Thalassemia 2006–2018: A Nationwide Population-Based Study." *J Clin Med.*, 2022.

[13] Jabbar HK, Hassan MK, Al-Naama LM., "Lipids profile in children and adolescents with β-thalassemia major." *Hematol Transfus Cell Ther*, pp. 01453-5, 2022.

[14] Hashemi A, Ghilian R, Golestan M, et al., "The Study of Growth in Thalassemic Patients and its Correlation with Serum Ferritin Level." *Iranian Journal of Pediatric Hematology Oncology*, pp. 147-151, 2011.

[15] Lidoriki I, Stavrou G, Schizas D, et al., "Nutritional Status in a Sample of Patients With β-Thalassemia Major." *Cureus*, 2022.

[16] Goldberg EK, Neogi S, Lal A, et al., "Nutritional Deficiencies Are Common in Patients with Transfusion-Dependent Thalassemia and Associated with Iron Overload." *J Food Nutr Res* (Newark), pp. 674-681, 2018.

[17] Sharma S, Bezboruah G., "Prevalence of short stature in transfusion dependent beta thalassemia patients in a tertiary care centre in North East India.", *Journal of Family Medicine and Primary Care*, pp. 2516-2520, 2022.

[18] Betts M, Flight PA, Paramore LC, Tian L, Milenkovi¢ D, Sheth S., "Systematic Literature Review of the Burden of Disease and Treatment for Transfusion-dependent β-Thalassemia." *Clinical Therapeutics*, pp. 322-337, 2020.

[19] Rathaur V, Imran A, Pathania, M., "Growth pattern in thalassemic children and their correlation with serum

ferritin.", *Journal of Family Medicine and Primary Care*, pp. 1166, 2020.
[20] Sengsuk C, Tangvarasittichai O, Chantanaskulwong P, Pimanprom A, Wantaneeyawong S, and Choowet A. "Association of iron overload with oxidative stress, hepatic damage and dyslipidemia in transfusion-dependent β-thalassemia/hbe patients." *Indian Journal of Clinical Biochemistry*, pp. 298-305, 2013.
[21] Elalfy MS, Ebeid FSE, el Gendy YG, et al., "Body Composition in Egyptian Children With Transfusion-dependent Thalassemia: The Impact of Nutrition and Metabolic Profile." *Journal of Pediatric Hematology/Oncology*, pp. 334–339, 2020.
[22] Setoodeh S, Khorsand M, Takhshid MA, "The effects of iron overload, insulin resistance and oxidative stress on metabolic disorders in patients with β-thalassemia major." *Journal of Diabetes & Metabolic Disorders*, pp. 767-774, 2020.
[23] Kamal M and Talal A, " Lipid profile in Jordanian children with β-thalassemia major.", *UHOD*, pp. 93-97, 2008.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 9230-9235, 2024
DOI: 10.55214/25768484.v8i6.3978