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Correlation between 25-Hydroxyvitamin D and Lipid Profile among Children with Beta Thalassemia Major

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Keywords: Thalassemia beta major; Lipid profile; vitamin D

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Abstract

BACKGROUND: Beta thalassemia major is associated with lipid profile abnormalities, presented as a lower level of total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoprotein (HDL), and higher triglyceride level; increasing risk for cardiovascular complications. The previous studies indicated that Vitamin D give a positive impact on the lipid profile in healthy children population. However, its role needs to be determined in a high-risk group of children with beta-thalassemia major.

AIM: To determine the correlation between vitamin D (25-OHD) and lipid profile among children with beta-thalassemia major.

METHODS: A cross-sectional study was conducted in a general tertiary hospital in Medan, Sumatera Utara, Indonesia from January to March 2018. Subjects were children aged below 18-year-old with beta-thalassemia major. The measurement of vitamin D (25-OHD) level and 10-12 hour overnight fasting serum lipid profile including total cholesterol, triglyceride, HDL, and LDL were performed. The analysis was done using Pearson's correlation and Fisher test. P value < 0.05 was considered significant.

RESULTS: Forty-five subjects were enrolled in this study, with serum ferritin level ranged from 1017 to 13372 ng/mL. The prevalence of vitamin D deficiency (a 25-OHD level less than 20 ng/mL) in this study was 40%, with mean value at 20.6 (SD 5.3) ng/mL. The markers for cardiovascular risk were observed to be elevated, both in Atherogenic Index Plasma (0.32 ± 0.25) and TC: HDL ratio (4.2 ± 1.5). Statistical analysis revealed that Vitamin D had positive correlation with total cholesterol ($r = 0.302$, $p = 0.044$) and HDL ($r = 0.297$, $p = 0.048$). There was no significant correlation between both vitamin D and triglyceride ($p = 0.305$), or vitamin D and LDL ($p = 0.727$).

CONCLUSION: Vitamin D correlated positively with total cholesterol and HDL in children with beta-thalassemia major. Positive correlation to HDL indicated a beneficial effect of vitamin D to reduce the risk of cardiovascular complication.

Introduction

Thalassemia beta was caused by a genetic disorder in globin β chain production. Complete loss of globin β chain presented as a β-thalassemia major [1]. Patients with β-thalassemia major need regular blood transfusion, arising complications from iron accumulation in heart, liver, and endocrine organs [2] [3]. It has been shown that children with β-thalassemia major develop premature atherosclerosis, as a result of chronic hemolysis and iron deposition in the blood vessels, along with dyslipidemia [3]. Children with β-thalassemia have abnormalities in lipid profile, presented as a lower level of total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoprotein (HDL), and higher triglyceride level [4].

Dyslipidemia in patients with β-thalassemia was caused by several factors; such as plasma dilution due to anaemia, increased erythropoietic activities followed by increased cholesterol uptake by macrophage and histiocyte in the reticuloendothelial system, liver impairment due to iron deposition, hormonal disturbance, and decreased extra-hepatic lipolysis activity [5]. The main factors contributing to dyslipidemia in a patient with β-thalassemia major are iron overload and oxidative stress [4].

The prevalence of Vitamin D deficiency in patients with beta-thalassemia major was reported as 5-87% worldwide [6]. It was more prevalent in children with beta-thalassemia aged above 10 years old [7] [8].

Vitamin D deficiency is associated with increased liver iron concentration, which impairs the hydroxylation process of Vitamin D by a 25-hydroxylase enzyme in the liver [9]. Vitamin D has been associated with the stiffness of blood vessels, which increased the risk of cardiovascular diseases and atherosclerosis [10].

Some previous studies revealed that vitamin D is associated with favourable lipid profile in children population [11]. Kelishadi et al. reported that vitamin D had an inverse correlation with total cholesterol, triglyceride, and LDL in healthy children population. Besides, there was a positive correlation between vitamin D level and HDL level [11]. Its favourable effect on lipid profile was associated with an increased level of calcium, parathyroid hormone suppression, and decreased insulin resistance [12] [13]. Vitamin D also maintain an adequate concentration of apolipoprotein A-1, which influences the formation of HDL [14]. The study by Hirschler reported that high dose vitamin D supplementation of 100.000 IU per month for 2 months is associated with a significant increase of HDL level and decreased triglyceride level in children [15]. However, the favourable effect of vitamin D to lipid profile in a high-risk group of children with beta-thalassemia major has not been extensively studied yet.

The objective of this study is to determine the correlation between vitamin D (25-OHD) and lipid profile among children with beta-thalassemia major

Methods

This study was an analytic observational study with a cross-sectional design. The data were collected from patients with β-Thalassemic Major in Haji Adam Malik General Hospital, Medan, Indonesia who receive a regular blood transfusion in one-day care ward from January until March 2018. The inclusion criteria were patients with β-Thalassemic Major diagnosed by haemoglobin electrophoresis, received regular blood transfusion, aged 1-18 years old, and serum ferritin level more than 1000 ng/ml. The exclusion criteria were patients with β-Thalassemic Major who already consumed vitamin D supplement or anti dyslipidemia drugs. The minimum sample required in this study was 42 subjects, calculated using the hypothesis test formula for correlation study with the power of 90 (β 10%).

The independent variables of this study was 25-hydroxyvitamin D, which was classifed as deficiency (less than 20 ng/mL), insufficiency (20-30 ng/mL), and normal (30-80 ng/ml). The dependent variable data were lipid profile, including total cholesterol, triglyceride, High Density Lipoproteins (HDL) and Low Density Lipoproteins (LDL). Triglyceride was classifed as normal (< 150 mg/dL) and high (≥ 150 mg/dL). Total cholesterol was classifed as normal (< 170 mg/dL), borderline (170–199 mg/dL), and high (≥ 200 mg/dL). HDL was classified as normal (> 40 mg/dL) and low (≤ 40 mg/dL). LDL was classified as normal (< 110 mg/dL), borderline (110-129 mg/dL), and high (≥ 130 mg/dL) [16].

The baseline data were obtained from subjects who fulfilled inclusion and exclusion criteria, including age, sex, weight, and length, the presence of organomegaly, Mid Upper Arm Circumference (MUAC), and serum ferritin within last 3 months before the study. The nutrition status of the subjects was plotted according to Weight for Length chart from WHO Child Growth Standard 2006 for children under 5 years old and CDC 2000 growth chart for children 5-18 years old.

The subject was requested to have 10-12 hours fasting before blood sampling, in which 3 ml of venous blood were extracted and collected in a serum tube. Measurement of 25-hydroxyvitamin D was performed via *chemiluminescence microparticle immunoassay* (CMIA) method. Measurement of triglyceride level was performed via glycerol phosphate oxidase method and cholesterol level via the enzymatic method. Measurement of HDL level was performed via accelerator selective detergent method and LDL level via the liquid selective detergent method. Instrument Architect (ABBOTT laboratories, USA) was used to perform all laboratory examinations. Pearson's correlation and Fisher exact test were used for statistical analyses by *SPSS Statistics ver. 20* software. Statistical significance was considered at p value less than 0.05. This study was approved by Ethics Committee of Faculty of Medicine, Universitas Sumatera Utara and Haji Adam Malik General Hospital.

Results

Out of 49 patients with β-thalassemia major, there were 45 subjects who fulfilled the inclusion and exclusion criteria. Four patients were excluded since the serum ferritin level was below 1000 ng/mL. There was a female preponderance of 56% in the subjects. The median age of the subjects was 10.9 years old, with the youngest subject of 1.6 years old and the oldest subject of 17.9 years old. The nutrition status of 47% of subjects was malnourished, and most of the subjects were stunted at 62% (Table 1).

All subjects had serum ferritin level above

1000 ng/mL with a median of 2000 ng/ml. This study reported the mean level of 25-hydroxyvitamin D in children with a β-thalassemia major at 20.6 ng/mL, with 55.6% of the subjects were in the insufficiency range (20-30 ng/mL).

Table 1: Clinical, Anthropometry, and Laboratory Parameters of Children with β-thalassemia major (n = 45)

Parameter	Value
Sex, n (%)	
Male	20 (44)
Female	25 (56)
Age (year), median (min-max)	10.9 (1.6 – 17.9)
Weight (kg), median (min-max)	24 (10 – 61)
Height (cm), mean (SD)	121.8 (± 23.53)
Mid upper arm circumference (cm), mean (SD)	17.28 (± 2.52)
Nutrition Status, n (%)	
Well-nourished	21 (47)
Malnourished	22 (49)
Overweight	2 (4)
Height for Age, n (%)	
Normal	16 (36)
Stunted	28 (62)
Severely Stunted	1 (2)
Serum Ferritin (ng/mL), median (min-max)	2000 (1017-13371.95)
Haemoglobin pre transfusion (g/dL), mean (SD)	6.9 (± 1.3)
25-hydroxyvitamin D (ng/mL), mean (SD)	20.6 (± 5.3)
Normal, n (%)	2 (4.4)
Insufficency, n (%)	25 (55.6)
Deficiency, n (%)	18 (40)
Triglyceride (mg/dL), median (Min-Max)	112 (64 - 287)
Normal, n (%)	34 (75.5)
High, n (%)	11 (24.5)
Total Cholesterol (mg/dL), mean (SD)	93.1 (± 21.4)
Normal, n (%)	45 (100)
Borderline, n (%)	0 (0)
High, n (%)	0 (0)
LDL (mg/dL), median (Min-Max)	57 (24 - 173)
Normal, n (%)	41 (91.2)
Borderline, n (%)	2 (4.4)
High, n (%)	2 (4.4)
HDL (mg/dL), mean (SD)	22.2 (± 6.1)
Normal, n (%)	0 (0)
Low, n (%)	45 (100)
Atherogenic Index Plasma, mean (SD)	0.32 (± 0.25)
Ratio Total Cholesterol: HDL, median (min-max)	4.4 (2.9-10.9)

Min = Minimum value; Max = Maximum value; SD = Standard Deviation.

The median of triglyceride and LDL were within normal range, at 112 mg/dL and 57 mg/dL respectively. The mean level of total cholesterol was within normal range at 93.1 mg/dL. However, the mean level of HDL was below the normal range at 22.2 mg/dL. Majority of the subjects had a normal level of triglyceride and LDL, at 75.5% and 91.2% respectively. All subjects in this study had a normal level of total cholesterol and low level of HDL. The markers for a predictor of cardiovascular diseases, Atherogenic Index Plasma (AIP) and total cholesterol to HDL ratio (TC: HDL), were shown in Table 1. Atherogenic Index Plasma was calculated by the formula log(Triglyceride: HDL), and the mean value was elevated at 0.32 (SD 0.25). The median value of TC: HDL was elevated too at 4.4 (range 2.9-10.9).

Table 2: Correlation between vitamin D and Lipid Profiles

		Triglyceride	Total Cholesterol	HDL	LDL
25-hydroxyvitamin D	r	-0.156	0,302	0,297	0,054
	p	0,305	0,044	0,048	0,727
	n	45	45	45	45

Pearson's test Confidence Interval 95%; r = correlation coefficient.

The correlation between 25-hydroxyvitamin D and lipid profile was shown in Table 2. Transformation data of triglyceride and LDL level were performed to make normal data distribution. Hence the Pearson's correlation was used in statistical analyses. Table 2 showed that there was no significant correlation between 25-hydroxyvitamin D and triglyceride level (p-value at 0.305) and LDL level (p-value at 0.727).

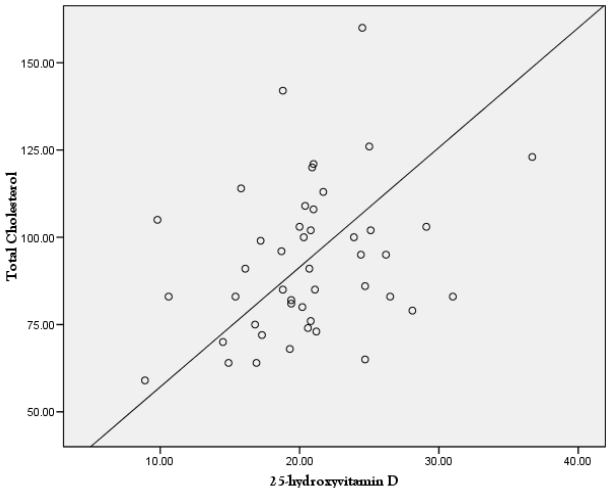

Figure 1: Scatter graph for correlation between 25-hydroxyvitamin D and total cholesterol

There was a significant correlation between 25-hydroxyvitamin D and total cholesterol level (p-value at 0.302). The correlation had a weak positive correlation coefficient (r = 0,302) as depicted in Figure 1. Besides, there was a weak positive correlation between 25-hydroxyvitamin D and HDL level (r=0,297) as depicted in Figure 2.

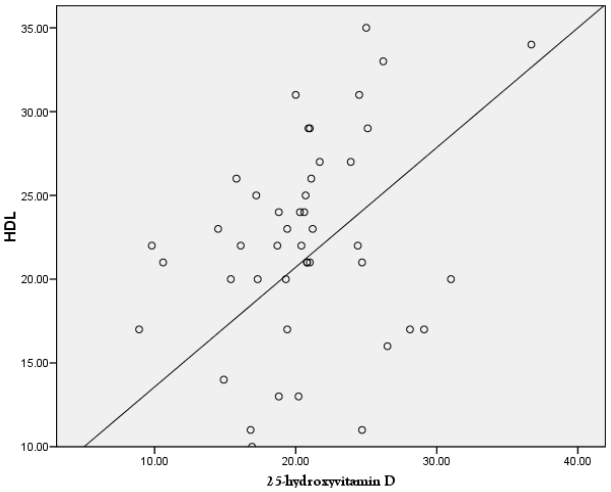

Figure 2: Scatter graph for correlation between 25-hydroxyvitamin D and HDL

Discussion

This study reported the prevalence of vitamin D deficiency at 40% and vitamin D insufficiency at 55.6% in children with beta-thalassemia major. This

result is in concordance with the previous study in Mesir by Fahim, who reported 37% of children with beta-thalassemia major had vitamin D deficiency, and another 54% had vitamin D deficiency [17]. The previous study in Indonesia by Fadillah reported a higher prevalence of vitamin D deficiency at 86% [18].

Up to 50-90% of Vitamin D is synthesised in the skin as the result of sun exposure, while the rest come from the diet. Vitamin D deficiency in a patient with beta thalassemia has been associated with liver iron accumulation, interfering with vitamin D hydroxylation [19]. Body iron accumulation in a patient with beta-thalassemia was monitored by serum ferritin measurement [18]. In this study, all subjects had high ferritin serum ranged from 1017 up to 13371.95 ng/mL, regardless of routine chelation therapy.

Serum iron deposition in the skin can cause hyperpigmentation, leading to the decreased conversion of 7-dehydrocholesterol to vitamin D3 in the skin. In tropical countries, vitamin D deficiency might occur as the children with beta-thalassemia was not allowed to play outside [6].

Dyslipidemia in children with beta-thalassemia major presented as a lower level of total cholesterol, HDL, and LDL; and higher triglyceride level compared to healthy child population [20] [21] [22]. Some factors contributing to dyslipidemia in thalassemia are plasma dilution due to anaemia and increased erythropoietic activity [5]. In this study, subjects had a low level of haemoglobin before blood transfusion at 6.9 g/dL (SD 1.3 g/dL). Increased erythropoietic activity will increase cholesterol uptake by macrophage and histiocyte within the reticuloendothelial system [5].

In this study, the mean or median level of total cholesterol, triglyceride, and LDL were still within normal range. Meanwhile, the HDL level was below the normal range (< 40 mg/dL). The mean value of HDL in this study at 22.2 (SD 6.1) mg/dL were much lower than a previous study by Fahim at 48.3 (SD 24.7) mg/dL [4]. Lipid profile abnormality which found in this study was low HDL level.

This study was not in agreement with previous studies, which reported that children with a β-thalassemia major in India, Egypt, and Jordania had high triglyceride level (> 150 mg/dL) [21] [22] [23] [24]. The decrease of triglyceride level was associated with decreased extra-hepatic lipolysis activities in children with beta-thalassemia [22] [23]. Another study in Iran and Italy reported that there was no significant difference between children with β-thalassemia major and healthy children control [25] [26]. The data from Southeast Asian is not available yet, prompting to further studies in the future.

All subjects in this study had HDL level below 40 mg/dL. The decrease of HDL level is associated with quick cleaning of activated monocyte and macrophage in a patient with beta-thalassemic major [24]. Pearson's statistic analyses in this study revealed a significant weak positive correlation between vitamin D and HDL level (r = 0,297); increase of vitamin D level was followed by an increase of HDL level. It was in agreement with the previous study in adult subjects by Saeidlou [13]. Vitamin D establish an adequate concentration of apolipoprotein A-1, which serves as a precursor of HDL formation [14]. The correlation coefficient in this study is more significant than the previous study in healthy children subjects by Kelishadi (r = 0.156) [11]. The studies in Iran dan Argentina reported that vitamin D supplementation 1000 IU daily or 100.000 IU per month was associated with an increase of HDL level [10] [15]. Hence, vitamin D supplementation in children with β thalassemia major is hypothesised to increase HDL level significantly.

In addition to low HDL level, subjects had a higher ratio of total cholesterol to HDL (TC: HDL) at 4.4. The upper limit for TC: HDL ratio is 3.5 based on Adult Treatment Panel III [20]. It is in agreement with the previous study by Ashar, who reported an increase of TC: HDL ratio at 5.7 in children with beta-thalassemia; increasing the risk of coronary heart diseases [20]. Another cardiovascular marker in this study, *Atherogenic Index Plasma* (AIP), was elevated at 0.32 (SD 0.25). Atherogenic Index Plasma value at more than 0.24 is a significant predictor for cardiovascular diseases [27]. The previous study by Sherief reported that high AIP level at 0.45 (SD 0.12) correlated with premature atherosclerosis in a patient with beta-thalassemia [5].

This study revealed the positive correlation between 25-hydroxyvitamin D and total cholesterol (r = 0,302). In contrast, the previous meta-analysis in healthy children population revealed a negative correlation between 25-hydroxyvitamin D and total cholesterol (r = -0,086) [11]. Vitamin D maintains a role in increasing calcium absorption in the digestive tract, through the formation of Calbindin (Calcium Binding Protein). Calbindin influences the influx of calcium into brush border of epithelial cells in the digestive tract through the diffusion process [28]. It was hypothesised that calcium binds the fatty acids from the diet into an insoluble form, which impair fat absorption in the digestive tract [12].

In children with beta-thalassemia major, iron overload and oxidative stress induce hypocholesterolemia [4]. In human, calcium acts as an inhibitor to the absorption of iron in the digestive tract. The absorption of iron in the digestive tract was conducted via Divalent Metal Transporter 1 (DMT 1) and Ferroportin (FPN) in the apical membrane. The interaction between calcium and DMT1 will inhibit the absorption of iron in the digestive tract [29]. It is hypothesised that iron absorption inhibition reduced iron overload and oxidate stress, which explained the positive correlation between 25-hydroxyvitamin D and total cholesterol in this study.

The strength of this study is the first study to

present the correlation between 25-hydroxyvitamin D and lipid profiles among a high-risk group of children with β-thalassemia major. There was an increase of markers for cardiovascular in the children with the β-thalassemia major; prompting to increase awareness of early cardiovascular diseases related to lipid profiles abnormalities. The limitation of this study is its inability to reveal a causal correlation between 25-hydroxyvitamin D and lipid profiles. The positive correlation between 25-hydroxyvitamin D and HDL need to be examined in the experimental study.

In conclusion, there is a significant positive correlation between 25-hydroxyvitamin D and lipid profiles in children with beta-thalassemia major, including total cholesterol and HDL level; but not with triglyceride and LDL level. Positive correlation to HDL indicated a beneficial effect of vitamin D to reduce the risk of cardiovascular complication. Further studies were needed to assess its causal correlation.

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