The differences of 25-Hydroxyvitamin D and malondialdehyde levels among thalassemia major and non-thalassemia

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The differences of 25-Hydroxyvitamin D and malondialdehyde levels among thalassemia major and non-thalassemia

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ABSTRACT

Background: Patients with thalassemia major who require regular blood transfusions, have experienced a decline in the level of 25-Hydroxyvitamin D and an increase in oxidative stress biomarkers, one of which is Malondialdehyde (MDA). Both mechanisms are thought to be associated with iron overload seen in transfusion-dependent thalassemia patients. It is necessary to research the differences in 25-hydroxyvitamin D and malondialdehyde levels among thalassemia major and non-thalassemia patients along with the increasing prevalence of thalassemia. The study aims to prove the differences in 25-hydroxyvitamin D and malondialdehyde levels among thalassemia major and non-thalassemia patients.

Methods: The study was an observational analytic study with cross sectional approach. Research subjects were 42 children consisting of 21 thalassemia major patients hospitalized at the Dr. R. Soedjati Grobogan Public Hospital and Dr. R. Soetrasno Rembang Public Hospital and 21 healthy children were matched for age. This study was conducted from March to September 2020. 25-Hydroxyvitamin D and malondialdehyde levels were examined using the enzyme-linked immunosorbent assay (ELISA) method and Thiobarbituric acid reactive substances (TBARS) method. Statistical analysis was done using Independent Sample T test and Mann-Whitney test, which $p<0.05$ was considered significant.

Results: There was no significant difference in the level of 25-hydroxyvitamin D ($p = 0.45$) in thalassemia major and non-thalassemia patients (25.96 ± 6.36 ng/mL and 27.54 ± 7.09 ng/mL respectively). There was a significant difference in the malondialdehyde level ($p = 0.00$) in thalassemia major and non-thalassemia patients (0.43 µmol/L and 0.14 µmol/L respectively).

Conclusion: Iron overload in patients with thalassemia major causes a decrease in 25-hydroxyvitamin D level. An insignificant difference in 25-hydroxyvitamin D level among thalassemia major and non-thalasemia indicates that other factors such as nutritional status, nutrient intake, and sun exposure also play an important role in 25-hydroxyvitamin D level. The formation of ROS triggered by iron overload also results in a significant increase of malondialdehyde level in thalassemia major.

Keywords: 25-Hydroxyvitamin D, Malondialdehyde, Thalassemia major.
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INTRODUCTION

Thalassemia is a genetic disorder inherited in an autosomal recessive manner in the form of a disturbance in the synthesis of blood hemoglobin due to a decrease or reduction in the production of one or more globin chains which causes erythrocytes to undergo intravascular hemolysis process and cause anemia of various degrees.[1] Thalassemia is differentiated according to its clinical manifestations into thalassemia major, thalassemia minor, and thalassemia intermedia.[2] Patients with thalassemia major usually experience severe anemia and depend on blood transfusions throughout their life, in contrast to patients with thalassemia minor and thalassemia intermedia who are clinically asymptomatic or have only mild to moderate anemia so that the need for blood transfusions varies.[3] Genes carrying major thalassemia traits are often found in Mediterranean countries, Middle East, and Southeast Asia including Indonesia. WHO states that around 7% of the world's population are carriers of thalassemia major and approximately 300,000 to 500,000 babies are born with thalassemia major each year.[4] In Indonesia, there is an increase in the number of thalassemia patients from 2012-2018 of 4.896 patients to 9.028 patients.[5]

Patients with thalassemia major require routine blood transfusions to survive in order to improve anemia due to decreased hemoglobin caused by ineffective erythropoiesis process. But on the other hand, repeated blood transfusion procedures will gradually cause excessive iron accumulation which can cause various clinical consequences.[6,7] Bone abnormalities such as osteoporosis

are one that is often found in patients with thalassemia major.[8]

Vitamin D has an important role in mineral balance and bone maintenance, which is related to calcium and phosphorus homeostasis.[9] Previous studies have shown that thalassemia patients who undergo repeated blood transfusions showed a significant decrease in vitamin D levels of around 90% and a decrease in calcium absorption as a result of iron accumulation in the body.[10] 25-Hydroxyvitamin D is the main form of vitamin D in the body's circulation, so its levels are used as a determinant of vitamin D status.[11]

In patients with thalassemia major who undergo routine blood transfusions, oxidative stress also occurs as a result of increased levels of free radicals and lipid peroxides which are believed to be associated with iron overload. Malondialdehyde (MDA) is the main product of lipid peroxidation in cells and is continuously produced in accordance with the proportion of lipid peroxidation that occurs so that MDA is used as a biological marker of oxidative stress. The accumulation of excess iron in thalassemia primary patients with repeated transfusions causes cells, especially erythrocytes to be susceptible to oxidative damage, increasing levels of lipid peroxidation markers such as MDA.[12,13] This study aims were to prove the differences in 25-hydroxyvitamin D and MDA levels among thalassemia major and non-thalassemia, in line with the increasing number of major thalassemia cases in Indonesia.

METHODS

This study was an analytic observational study with a cross sectional approach which was conducted from March to September 2020.

There were 42 research subjects taken by consecutive sampling, consisted of 21 thalassemia major patients who had routine blood transfusions at Dr. R. Soedjati Grobogan Public Hospital and dr. R. Soetrasno Rembang Public Hospital and 21 healthy populations of equal age (non-thalassemia) who met the inclusion and exclusion criteria. This study's inclusion criteria were male and female thalassemia major and non-thalassemia patients aged 2-20 years, thalassemia major patients who had received blood transfusions >10 times, and were willing to become research respondents. Subjects who experienced fever, leukocytosis, and received vitamin D and calcium supplementation were excluded from the study.

Written informed consent was obtained from parents/guardians. Furthermore, data were obtained from anamnesis with questionnaires, physical examination, and laboratory examinations of venous blood samples. The dependent variables in this study were 25-hydroxyvitamin D and malondialdehyde levels. The examination of 25-hydroxyvitamin D level was carried out at the Iodine Deficiency Disorder Laboratory, Faculty of Medicine, Diponegoro University using the ELISA method, while the examination of malondialdehyde level was carried out at the Clinical Pathology Laboratory of the Diponegoro National Hospital using the TBARS method using TCA and TBA reagents.

The data obtained were then analyzed statistically using the SPSS program. A descriptive test was carried out on each data, then tested for data normality using the Shapiro-Wilk test. Data of 25-hydroxyvitamin D level were normally distributed, so the test was continued using Independent Sample T test. Data of malondialdehyde level were not normally distributed, so the test was continued using Mann-Whitney test. Spearman Correlation test was performed on sun exposure data as a confounding variable for 25-hydroxyvitamin D level. The statistical test result was considered significant if $p < 0.05$.

RESULTS

Out of 62 research subjects, there were 42 subjects who met the inclusion and exclusion criteria consisted of 21 thalassemia major and 21 non-thalassemia subjects. The characteristics of the research subjects can be seen in Table 1.

From the total of research subjects, the composition of thalassemia major subjects consisted of 9 males (42.9%) and 12 females (57.1%), while non-thalassemia subjects consisted of 10 males (47.6%) and 11 females (52.4%). The mean age of

Table 1. Characteristics of the research subjects

Variable	Mean ± SD	n (%)	
Age			
- Thalassemia major	11.33 ± 3.71		
- Non thalassemia	9.10 ± 3.55		
Gender		Thalassemia major	Non thalassemia
		9 (42.9%)	10 (47.6%)
- Male		12 (57.1%)	11 (52.4%)
- Female			
25-Hydroxyvitamin D levels (ng/mL)			
- Normal (>30 ng/mL)		5 (23.8%)	4 (19.0%)
- Insufficiency (20-30 ng/mL)		13 (61.9%)	14 (66.7%)
- Deficiency (<20 ng/mL)		3 (14.3%)	3 (14.3%)

Table 2. Descriptive analysis and difference tests of 25-hydroxyvitamin D and malondialdehyde levels

Variable	Mean ± SD	Median (Min-Max)	*p*
25-Hydroxyvitamin D levels (ng/mL)			0.45[a]
Thalassemia major	25.96 ± 6.36		
Non-thalassemia	27.54 ± 7.09		
Malondialdehyde levels (µmol/L)			0.00[b*]
Thalassemia major		0.43 (0.08-2.34)	
Non-thalassemia		0.14 (0.03-0.30)	

[a], Independent Sample T test; [b*], Mann-Whitney test, significant

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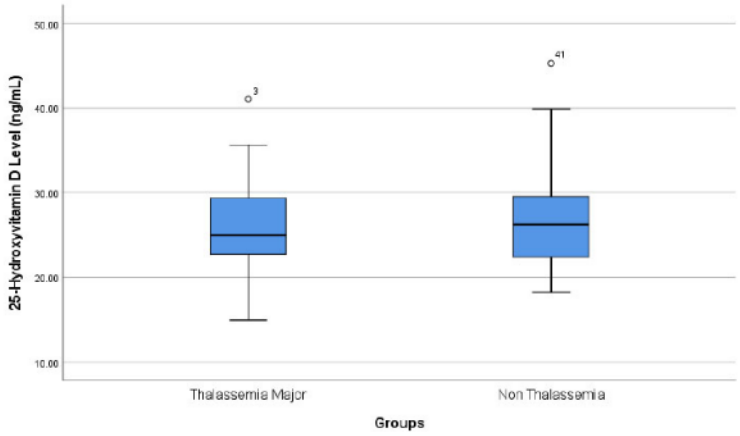

Figure 1. Box plot graphic of 25-hydroxyvitamin D levels in thalassemia major and non thalassemia.

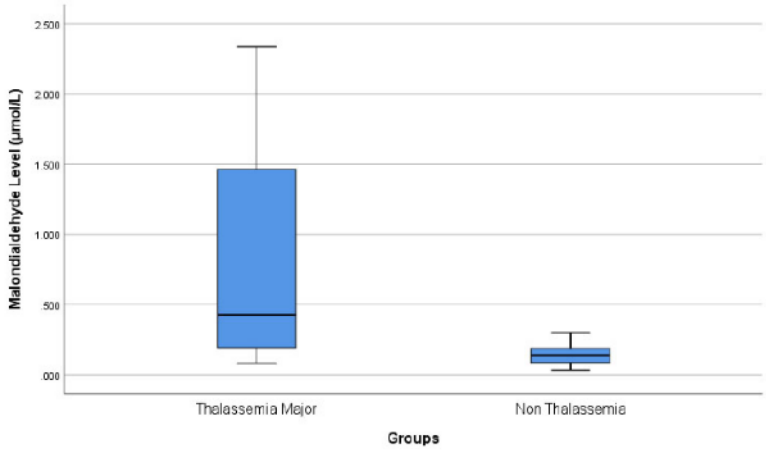

Figure 2. Box plot graphic of malondialdehyde levels in thalassemia major and non thalassemia.

Table 3. Analysis of sun exposure on 25-hydroxyvitamin D level

	25-hydroxyvitamin D level (ng/mL) (Mean ± SD = 26.75 ± 6.70)
Sun exposure (hour) (Median [(Min-Max) = 1.00 (0.00-4.00)]	r = 0.39
	p = 0.81
	n = 42

p, Spearman Correlation Test; r = correlation coefficient

thalassemia major subjects (11.33 ± 3.71 years) showed a higher number compared to non-thalassemia subjects (9.10 ± 3.55 years). In thalassemia major group, 3 subjects (14.3%) had deficient, 13 subjects (61.9%) had insufficient, and 5 subjects (23.8%) had normal 25-hydroxyvitamin D levels while in non-thalassemia group, 3 subjects (14.3%) had deficient, 14 subjects (66.7%) had insufficient, and 4 subjects (19.0%) had normal levels of 25-hydroxyvitamin D.

The normality test was performed using the Shapiro-Wilk test because the number of sample was less than 50. The results of descriptive analysis and different tests of thalassemia major and non-thalassemia on 25-hydroxyvitamin D and malondialdehyde levels are presented in Table 2.

25-Hydroxyvitamin D level in thalassemia major had a mean value of 25.96 ± 6.36 ng/mL. The mean value of 25-hydroxyvitamin D level in non-thalasemia was 27.54 ± 7.09 ng/mL. The normality test by Shapiro-Wilk test showed p-value > 0.05 (p = 0.87 and 0.07), which indicated that the data were normally distributed. So, the test was continued with the Independent Sample T test. The test result was not significant with p = 0.45, which indicated no significant difference in 25-hydroxyvitamin D level among thalassemia major and non-thalassemia. Data distribution of 25-hydroxyvitamin D levels in thalassemia major and non thalassemia is presented in Figure 1.

Analysis of sun exposure as a confounding variable on 25-hydroxyvitamin D levels was initiated by a normality test using the Shapiro-Wilk test. The results of the normality test showed p <0.05 (p = 0.00) in sun exposure data, which indicated that the data was not normally distributed, so the test was continued with the Spearman Correlation test. The results of the analysis of sun exposure on 25-hydroxyvitamin D level are shown in Table 3.

The median value of sun exposure data of the total subjects was 1.00 hour with the mean value of 25-hydroxyvitamin D was 26.75 ± 6.70 ng/mL. The result of Spearman Correlation test was p = 0.81, which showed that there was no significant correlation between sun exposure and 25-hydroxyvitamin D level with a statistically weak positive correlation coefficient (r = 0.39).

Malondialdehyde level in thalassemia major had a median value of 0.43 µmol/L, with a minimum value of 0.08 µmol/L and a maximum value of 2.34 µmol/L while the median value of malondialdehyde level in non-thalassemia was 0.14 µmol/L, with a minimum value of 0.03 µmol/L and a maximum value of 0.30 µmol/L. The results of the normality test with

the Shapiro-Wilk test showed p <0.05 in major thalassemia group (p = 0.01), which indicated that the data were not normally distributed. The data transformation had been carried out, but the data distribution remained abnormal. The difference test was performed using the Mann-Whitney test. The result obtained was p = 0.00 which indicated a significant difference in malondialdehyde level among thalassemia major and non thalassemia. Data distribution of malondialdehyde levels in thalassemia major and non thalassemia is presented in Figure 2.

DISCUSSION

This study involved 42 subjects consisted of 21 thalassemia major patients and 21 non-thalassemia patients. From 2 groups of research subjects, the number of subjects with female gender was more than male. This was also reported in Nasir's (2018) study, which obtained more female thalassemia major subjects than the male.[14] The mean age of thalassemia major subjects was 11.33 ± 3.71 years, while the mean age of the non thalassemia subjects was 9.10 ± 3.55 years. This is according to the study of Permatasari et al, which obtained the most age-related subjects of thalassemia major in the age range of 6-15 years.[15] Patients with thalassemia major usually tend to appear normal at birth and then clinical conditions are found in the range of age that is getting worse even though clinical symptoms have appeared since the age of 1-2 years.[16]

The results showed that the mean value of 25-hydroxyvitamin D level in thalassemia major was 25.96 ± 6.36 ng/mL and non-thalassemia was 27.54 ± 7.09 ng/mL. This figure shows that the mean value of 25-hydroxyvitamin D level in thalassemia major is lower than non thalassemia. However, the statistical test results indicated that there was no significant difference in the level of 25-hydroxyvitamin D between the thalassemia major and non thalassemia groups (p = 0.45). The results obtained in this study are in accordance with the research of Abbassy et al. and Madhu et al. which showed that there was no significant difference in the levels of 25-hydroxyvitamin D between thalassemia major and non thalassemia patients.[17,18]

In patients with thalassemia major who routinely undergo blood transfusions, there was decrease in circulating serum levels of vitamin D, especially 25-hydroxyvitamin D, this associated with excess iron accumulation in the body, which will cause disruption in the vitamin D hydroxylation process if it accumulates in the liver.[19] Excess iron accumulation in the skin can also cause reduced conversion of 7-dehydrocholesterol to vitamin D3, resulting in a synthesis defect.[14]

Furthermore, the decrease in 25-hydroxyvitamin D levels can also be influenced by other factors. Herawati et al. reported that nutrient intake, especially energy, protein, and fat were related to vitamin D levels.[19] The ineffective erythropoiesis that occurs in thalassemia results in increased energy expenditure and protein turnover. Protein is needed either in the form of an enzyme, vitamin D receptor (VDR), or vitamin D binding protein (VDP) which carries 95-99% of the total 25-hydroxyvitamin D.[19] Nicholas et al. also mentioned that protein sources such as fish, fortified milk, and meat are proven to be the main sources of vitamin D3 (cholecalciferol) which can suppress the activity of the DHCR7 gene which regulates the enzyme that converts 7-dehydrocholesterol into cholesterol in the skin, thus affecting vitamin D levels.[20] Fat in 15-30% of total consumption from total calories is considered to have a positive correlation with vitamin D levels, wherein this amount fat functions best in helping the absorption of vitamin D.[19] In addition, low levels of vitamin D are also associated with nutritional status, where the risk is increased in overweight or obese children. Its mechanism is believed to be related with fat-soluble characteristic of vitamin D.[21]

Sun exposure also counts as one of the factors that can affect the 25-hydroxyvitamin D level. The results of this study showed that the median value of sun exposure of the total subjects was 1.00 hour, but the correlation between sun exposure and 25-hydroxyvitamin D level was not statistically significant (p = 0.81). This can occur due to other factors affecting sun exposure. Some studies have found that genetic and cultural factors such as dark skin and wearing closed clothes can inhibit sun exposure and increasing the risk of low 25-hydroxyvitamin D levels. Other than that, the lack of outdoor physical activity and sunscreen use is also associated with inhibition of the synthesis of vitamin D from sunlight on the skin.[19,22]

Malondialdehyde (MDA) is a secondary product compound from lipid peroxidation which is reactive and is often used as a biological marker of oxidative stress. In this study, the results of the median value of MDA level in thalassemia major was 0.43 µmol/L and non thalassemia was 0.14 µmol/L. From these results, it is known that MDA level in thalassemia major showed a higher value than the MDA level in non thalassemia, with a statistically significant difference (p = 0.00). These results are consistent with the studies of Sengsuk et al. and Mahdi et al. who reported significantly higher levels of MDA in thalassemia major with repeated transfusions compared to non thalassemia.[23,24]

The ineffective erythropoiesis due to disturbances in β-globin chain synthesis plays a vital role in the occurrence of oxidative stress in thalassemia patients. The decrease in β globin chains synthesis causes the accumulation of free α globin chains which is unstable and triggers the destruction of red blood cells and the release of iron in the reactive form of heme. This causes excess iron accumulation, especially in patients with thalassemia major who undergo repeated transfusions.[23,24] This is also supported by Cighetti et al. who reported that MDA levels were found to be higher in major thalassemia patients who received routine blood transfusions compared to thalassemia intermediate patients.[25]

The accumulation of excess iron that occurs both in blood plasma and intracellular will cause the formation of ROS compounds which will disrupt the integrity of cell membranes including erythrocytes, such as superoxide anions ($O2^{-}$), hydrogen peroxides (H_2O_2), and especially hydroxyl radicals (OH^{-}).[24] The aggression of ROS compounds, especially hydroxyl radicals, results in the breaking of the polyunsaturated fatty acid (PUFA) chain contained in the cell membrane structure so that a lipid peroxidation chain reaction is formed which produces toxic

compounds, one of them is MDA as the end product of the reaction.[26]

CONCLUSION AND SUGGESTION

Iron overload in patients with thalassemia major causes a decrease in 25-hydroxyvitamin D level. An insignificant difference in 25-hydroxyvitamin D level among thalassemia major and non-thalasemia indicates that other factors such as nutritional status, nutrient intake, and sun exposure also play an important role in 25-hydroxyvitamin D level. The formation of ROS triggered by iron overload also results in a significant increase of malondialdehyde level in thalassemia major. Researchers suggest that further research should be undergone to investigate nutritional status, nutrient intake, and factors associated with sun exposure so that its effect on 25-hydroxyvitamin D levels in thalassemia can be considered.

CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of this article.

ETHICAL STATEMENT

This study has received permission from the Health Research Ethics Commission (KEPK), Faculty of Medicine, Universitas Diponegoro with ethical clearance reference number: 113/EC /KEPK/FK-UNDIP/VI/2020. All study protocol in accordance to Helsinki Declaration of huan right.

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AUTHOR CONTRIBUTION

All authors had contributed equally in project administration, writing the original draft, and agree for the final version of the manuscript for final publication.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6