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Original Article

Transfusion frequency, ferritin, and carotid intima media thickness in transfusion-dependent thalassemia patients

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Abstract

Introduction: The carotid tunica intima-media thickness (cIMT) is an early marker of atherosclerosis and associated with an increased risk of cardiovascular diseases. Endothelial dysfunction also contributed with the increased cardiovascular risk in thalassemia caused by iron accumulation, reduced nitric oxide, and increased lipid peroxidation. Studies about atherosclerosis markers in thalassemia patients show inconsistent results.

Aim: This research assesses cIMT in transfusion-dependent thalassemia patients and examines its relationship with clinical and laboratory parameters.

Materials and methods: This was a cross-sectional study that was conducted from March to May 2024, in the Therapy and Thalassemia Clinics, Universitas Indonesia Hospital. Ultrasound cIMT measurements were recorded for both the left and right distal common carotid artery walls, 5 mm proximal to the bifurcation. The cIMT diameters were collected from each wall and mean thickness values from both sides.

Results: This study included 25 adult thalassemia patients who were diagnosed with transfusion-dependent thalassemia. Most subjects were male, with a median age of 25 years, and had an underweight BMI. Patients with underweight BMI had thicker cIMT, both in mean and maximum diameter (p=0.008 and p=0.011, respectively).

Conclusion: Additionally, a transfusion frequency of ≥3 per month had a greater maximum diameter cIMT (p=0.046). A moderate positive correlation was observed between average ferritin levels and maximum intima-media thickness (r=0.402, p=0.046).

Keywords

carotid intima media thickness, cardiovascular risk, transfusion-dependent thalassemia

Introduction

Pre-clinical atherosclerosis had higher stroke and cardiovascular (CV) morbidity. Carotid tunica intima-media thickness (cIMT) is a marker of subclinical organ damage and is an independent predictor of CV risk. A study had reported that cIMT had higher sensitivity in detecting subclinical atherosclerosis compared with coronary calcium score.[1] Carotid tunica intima-media thickness is also associated with traditional CV risk factors, such as age, sex,

smoking, dyslipidemia, and obesity.[1] The measurement of cIMT is a non-invasive and easily performed procedure using B-mode ultrasound of the carotid artery in the neck.[2] Identifying early atherosclerosis marker give opportunity for early intervention in high-risk CV subjects, including transfusion-dependent thalassemia patient.[3]

Cardiovascular disease is the most common cause of morbidity and mortality in thalassemia patients. Cardiac abnormalities are primarily due to iron overload in the heart, leading to cardiomyopathy. Association between iron load and risk of atherosclerosis also had been studied in thalassemia patient.[3] Another pathogenesis is caused by untreated anemia, which is followed by tissue hypoxia increasing pulmonary resistance and causing pulmonary hypertension. Endothelial dysfunction also contributed to CV in thalassemia caused by iron accumulation, reduced nitric oxide, and increased lipid peroxidation. Chronic inflammation from multiple transfusions, infections, and stromal cell hyperplasia also results in vascular damage.[4]

Studies about subclinical atherosclerosis markers in thalassemia patients show inconsistent results.

Aim

This research assesses cIMT in transfusion-dependent thalassemia patients and examines its relationship with clinical and laboratory parameters at Universitas Indonesia Hospital.

Methods

Study design and participant

This study was a cross-sectional study conducted from March to May 2024, in the Therapy and Thalassemia Clinics, Universitas Indonesia Hospital. Study participants were adult transfusion-dependent thalassemia patients.

Data collection and cIMT measurement

Clinicals data obtained from medical records included age, body weight, height, mean Hb levels over the past two months, packed red cells volume per kg body weight received for previous two months, and average ferritin levels over six months. The measurement of cIMT was performed after blood transfusion, performed by internist-cardiovascular consultant, using techniques in line with the 2012 Mannheim Carotid Intima-Media Thickness and Plaque Consensus. The carotid intima-media thickness was visualized as a double-line pattern between the intima-lumen and media-adventitia interfaces of the carotid artery in a longitudinal view using B-mode ultrasound. The measurement was taken near the carotid bifurcation at a plaque-free area in the distal common carotid artery segment. The artery wall was examined at a lateral probe position with a 90-degree insonation angle. Measurements were recorded for both the left and right distal common carotid artery walls, 5 mm proximal to the bifurcation. Data about cIMT diameter were collected for each wall and mean thickness values from both sides.[5,6]

Data analysis

Data analysis was performed using SPSS v. 28. Categorical data were shown in proportions, while numerical data were presented as mean or median. The Mann-Whitney test was used to assess rank differences of cIMT by age group, sex, body mass index (BMI), and packed red cell volume per kg body weight over the last two months. Spearman correlation tests examined relationship between Hb, ferritin, and cIMT (both maximum and mean diameter).

Ethical approval

Ethical approval for the study was obtained from the Ethics Committee of FMUI, Ethics number KET-263/UN2.F1/ETIK/PPM.00.02/2024.

Results

This study included 25 adult thalassemia patients who had transfusion-dependent thalassemia in the thalassemia clinic of Universitas Indonesia Hospital. The subjects had a median age of 25 years, 60% of them were male, and had an underweight BMI. The majority of subjects underwent blood transfusions 1-2 times per month. Participant characteristics are shown in **Table 1**.

Table 1. Subject characteristics

Clinical characteristics	Results
Age, median, year	25.0 (18.0–68.0)
Sex	
Male, n (%)	15 (60.0)
BMI	
Underweight, n (%)	52.0
Normoweight, n (%)	48.0
Transfusion frequency /month	
1-2, n (%)	52.0
≥3, n (%)	48.0
Pre-transfusion hemoglobin level (mean/2 month), mean, g/dL	8.55±0.76
Packed red cell volume in the last 2 months, mean, ml/kg BW	7.04±1.32
Ferritin level, mean last 6 months, ng/mL	5535.88±2792.67
Mean diameter cIMT, median, mm	0.40 (0.03–0.06)
Maximum diameter cIMT, median, mm	0.50 (0.04–0.70)

Based on clinical characteristics, the distribution of cIMT showed that patients with an underweight BMI had thicker tunica intima-media, both in mean and maximum values (p=0.008 and p=0.011, respectively). Additionally, participants with a transfusion frequency of ≥3 per month had greater maximum diameter cIMT (p=0.046) **(Table 2).**

A correlation test was conducted between the mean Hb levels, packed red cell volume, and ferritin levels with the mean and maximum diameter of carotid intima-media thickness **(Table 3)**. A moderate positive correlation was observed between average ferritin levels and maximum intima-media thickness (r=0.402, p=0.046).

The scatter plot of Spearman correlation test between the mean ferritin and the maximum thickness of the intima media can be seen in **Fig. 1**.

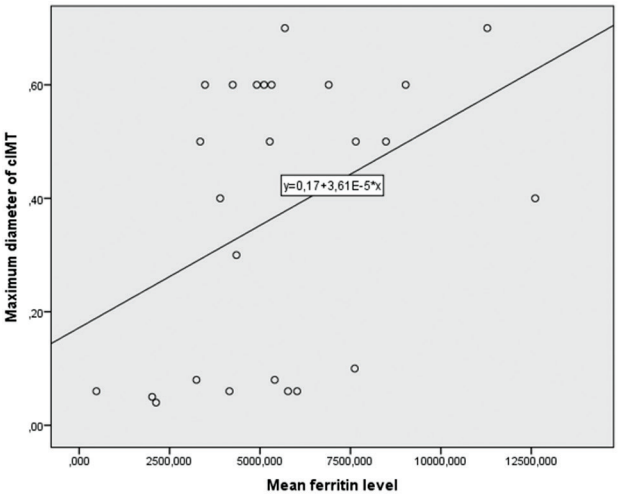

Figure 1. Correlation of mean ferritin levels in the last 6 months and maximum diameter of cIMT.

Discussion

The mean pre-transfusion Hb level in this study was 8.55±0.76 g/dl, consistent with reports of thalassemia in Indonesia, which still faces a challenge in implementing the pre-transfusion Hb target of >9 g/dl, as well as poor adherence to iron chelation therapy.

Subject characteristics

In this study, most subjects were male (60.0%) with a median age of 25 years (18.0–68.0), and an underweight nutritional status (52.0%). The mean pre-transfusion Hb level

Table 2. Clinical characteristics and cIMT diameter

Clinical characteristics	cIMT			
	Mean	*p*	Maximum	*p*
Age		0.894		0.611
<25 years, n (%)	0.40 (0.04–0.60)		0.45 (0.05–0.60)	
≥25 years, n (%)	0.40 (0.03–0.60)		0.50 (0.04–0.70)	
Sex		0.091		0.115
Male, n (%)	0.45 (0.06–0.60)		0.50 (0.06–0.70)	
Female, n (%)	0.23 (0.03–0.50)		0.25 (0.04–0.60)	
BMI, n (%		0.008		0.011
Underweight, n (%)	0.45 (0.06–0.60)		0.60 (0.06–0.70)	
Normoweight, n (%)	0.09 (0.03–0.50)		0.09 (0.04–0.60)	
Transfusion frequency /month		0.046		0.068
1-2, n (%)	0.10 (0.04–0.50)		0.10 (0.05–0.60)	
≥3, n (%)	0.45 (0.03–0.60)		0.55 (0.04–0.70)	

Table 3. Spearman correlation between clinical characteristics and cIMT diameter

Clinical characteristics	cIMT			
	Mean	*p*	Maximum	*p*
Pre-transfusion hemoglobin level (mean/2 month), mean, g/dL	−0.155	0.459	−0.097	0.646
Packed red cell volume in the last 2 months, mean, ml/kgBW	0.208	0.319	0.327	0.111
Ferritin level, mean last 6 months, ng/mL	0.292	0.157	0.402	0.046

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in this study was 8.55±0.76 g/dl, consistent with reports of thalassemia in Indonesia, which still faces a challenge in implementing the pre-transfusion Hb target of >9 g/dl, as well as poor adherence to iron chelation therapy.[7] The mean ferritin level in this study was 5535.88±2792.67 ng/mL, which aligns with literature indicating that the proportion of subjects with ferritin levels >4000 ng/mL is higher in the Asia-Pacific and Middle East regions compared to Europe.[8]

The median maximum diameter of cIMT observed in this study was 0.5 mm, which was larger than the 75th percentile diameter for populations under 30 years of age, both male (right carotid 0.48 mm, left carotid 0.49 mm) and female (right carotid 0.43 mm, left carotid 0.47 mm).[9] Thalassemia has been associated with increased cIMT. Intravascular hemolysis in thalassemia would lead into increased free heme levels in the circulation. Free heme, a pro-atherogenic free radical, increases endothelial permeability, smooth muscle proliferation, and LDL oxidation.[10] In thalassemia patients, the hemopexin levels, a glycoprotein that binds free heme, are also reduced, leading to higher free heme levels.[11]

In this study, 52% of patients had underweight BMI, which is a higher proportion compared with other studies that reported 40% of subjects were underweight. Underweight in thalassemia patients had shown due to low percentage of body fat. Low body fat had been associated also with low bone mass in thalassemia patients.[12] The pathogenesis of low BMI and altered body composition had multiple risk factors such as nutritional deficiency, chronic anemia and hypoxia, iron overload, inadequate use of chelating agents, and endocrinopathies.[13]

Nutritional status and cIMT

This study found that subjects with an underweight BMI had thicker cIMT compared with those with a normal BMI. This finding aligns with the conclusions of previous studies, which indicated that patients with malnutrition exhibit thicker intima-media layers in comparison to those with adequate nutritional status.[14-16] The relationship between malnutrition and increased cardiovascular risk, including cIMT, is associated with heightened systemic inflammation. Previous study reported that systemic inflammation was linked to malnutrition, marked by decreased prealbumin and albumin levels.[16] Increased oxidative stress markers in thalassemia patients had been associated with elevated resting energy expenditure and eventually with being underweight. Meanwhile, oxidative stress had been associated with increased cIMT.[13,17]

Transfusion characteristics and cIMT

Increased transfusion frequency has been linked to iron overload. Each unit of packed red cells is estimated to contain 200-250 mg of iron. Inadequate transfusion volume leads to more frequent transfusions. Studies have shown that patients with lower pre-transfusion Hb targets are associated with more frequent transfusions and increased iron levels compared with patients with higher pre-transfusion Hb targets. A lower pre-transfusion hemoglobin (Hb) level has been shown to be associated with hypersplenism, which has the potential to complicate the achievement of the pre-transfusion target level.[18] Transfusions cause a temporary increase in serum iron and transferrin saturation within the first 24 hours, persisting up to 36 hours post-transfusion.[19] Conversely, frequent blood donors had been shown thinner tunica intima-media thickness, as blood donation lowers body iron levels, and also ferritin and hepcidin level.[20,21]

Iron overload and cIMT

Higher ferritin levels in thalassemia patients have been associated with increased intima-media thickness in previous studies.[10,22] Ferritin is a marker of iron overload in thalassemia patients. The iron overload condition has been known to be linked to increased free iron radicals, which heighten oxidative stress. Increased iron followed with increased reactive oxygen species formation, especially hydroxyl radicals. Hydroxyl radicals could oxidize low-density lipoprotein, which would initiate foam cell formation, and eventually atherosclerosis.[20,21] Elevated free iron radicals cause endothelial injury and accelerating atherosclerosis.[21] Jindal et al.[17] had reported that lipid peroxidation product malondialdehyde (MDA) increased in thalassemia patients. The study also reported correlation between MDA and cIMT in thalassemia subjects.

Increased ferritin also followed with increased hepcidin which caused iron retention in macrophages. The process of iron retention within the macrophages has been demonstrated to result in an increase in oxidative stress and lipid oxidation.[23] Macrophage iron content had been known as a determinant factor in atherosclerotic plaque progression.[24]

Study limitation and strengths

The present study was subject to several limitations. Primarily, it was a single-center study with a limited sample size. There were several parameter that were not evaluated in this study, such as albumin and cardiac MRI T2. This study result highlights the importance of intervention not only for iron overload but also for nutrition among transfusion-dependent thalassemia patients, which may lead to a reduction in subclinical atherosclerosis and cardiovascular disease risk.

Conclusion

This study found that among the transfusion-dependent thalassemia patients, those with underweight BMI and transfusion frequency of ≥3 times per month had thicker intima-media layers. Ferritin levels also showed a moderate positive correlation with the maximum diameter of cIMT.

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Competing interests

the authors have declared that no competing interests exist.

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