

## Original Article

## The correlation between ferritin level and cardiac dysfunction in patients with thalassemia

Fajar Subroto, MD; Bulan Ginting Munthe, MD; Najib Advani, MD; Agus Firmansyah, MD, PhD

### ABSTRACT

**Background** Patients with  $\beta$ -thalassemia major, long-term transfusion, extravasal hemolytic, and increased intestinal absorption of iron result in systemic iron overload, which may accumulate in myocardium causing cardiac dysfunctions. Congestive heart failure usually develops in adolescence or early adult years, and patient usually dies within 1 year after the onset of symptoms. Therefore, it is important to detect early signs of cardiac dysfunction in patient with thalassemia.

**Objective** This study aimed to assess the correlation between ferritin level and cardiac dysfunction in patients with thalassemia. **Methods** A cross sectional study was conducted on 62  $\beta$ -thalassemic patients (34 males and 28 females) with age ranging from 3.5 to 23 years. They received 3,150 – 94,985 mL of blood; with the serum ferritin level of 812.2 – 12,175 ng/mL. Each patient underwent laboratory examinations and clinical cardiac evaluation with ECG and echocardiography.

**Results** Cumulative blood transfusions correlated well with the serum ferritin values ( $p=0.001$ ). The serum ferritin level did not show correlation with deferoxamine (DFO) treatment. ECG examination revealed 5 patients (8.1%) with dysrhythmia, LVH, and heart block grade II and I. Echocardiography examination showed 18 patients (29%) with systolic or diastolic dysfunction. There was no correlation between the serum ferritin level and cardiac dysfunctions ( $p=0.640$ ). The serum ferritin prediction value against cardiac dysfunctions could not be established.

**Conclusion** There was no correlation between serum ferritin levels with cardiac dysfunctions. In detecting cardiac dysfunctions in thalassemic patients, echocardiography was more sensitive than ECG [Paediatr Indones 2003;43:24-27].

**Keywords:** thalassemia, iron overload, ferritin, cardiac dysfunctions, ECG, echocardiography.

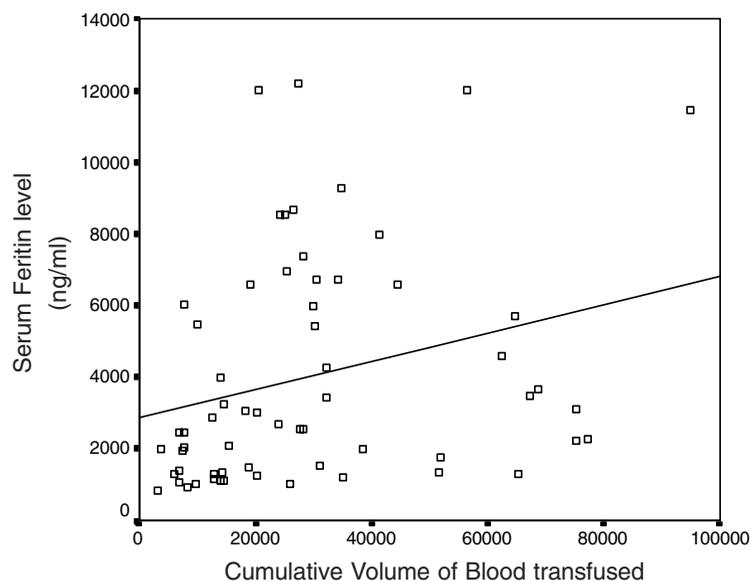
Patients with  $\beta$ -thalassemia major, long-term transfusion, extravasal hemolysis, and increased intestinal absorption of iron result in systemic iron overload.<sup>1</sup> A large excessive of steadily iron storage accumulation that will

progressively damage the organs is called hemochromatosis.<sup>2-6</sup> The deposition of iron in myocardium causes cardiac dysfunctions. When cardiac impairment caused by iron deposition is severe enough to be clinically obvious, the disease is advanced and the subsequent survival is brief, congestive heart failure develops usually in adolescence or early adult years, and patient usually dies within 1 year after the onset of symptoms.<sup>7,8</sup> Therefore, it is important to detect early signs of cardiac dysfunction in patient with thalassemia.

The serum ferritin concentration correlates well with the deposited iron in the tissue. Measurement of serum ferritin has been a valuable tool for evaluating iron status clinically and has been used as a marker in many screening studies.<sup>9-11</sup> ECG and roentgenography are relatively insensitive in detecting cardiac dysfunction before the onset of clinically apparent disease. Echocardiography permits detection of anatomic and functional abnormalities before the onset of abnormalities detectable with ECG and roentgenography.<sup>12,13</sup> This study aimed to assess the correlation between ferritin level and cardiac dysfunction in patients with thalassemia.

From the Division of Hematology and Cardiology, Department of Child Health, Medical School, University of Indonesia—Cipto Mangunkusumo Hospital, Jakarta.

**Reprint requests to:** Fajar Subroto, MD, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Tel. 62-21-390 7740, Fax, 62-21-390 7743.



**Figure 1.** Correlation between serum ferritin with cumulative blood transfusions

## Methods

Sixty two consecutive patients (34 males, 28 females) with b-thalassemia major were studied from February–November 2001. All patients regularly visited the Thalassemia Center, Department of Child Health, Cipto Mangunkusumo Hospital. The inclusion criteria were absence of cardiac symptoms or clinically apparent heart disease and had received a minimal of 10 units transfusion. None of the patients was treated with cardioactive medications. The mean of age was 11.5 (range 3.5-23; SD 5.2) years. Transfusion therapy had been started at the age range of 2 month to 10 years. At the time of the cardiac evaluation done, cumulative transfusion loads varied from 3.150 to 94.985 mL, with ferritin level of 812.2 – 12.175 ng/mL. Eleven patients had iron chelation treatment with deferoxamine with optimal compliance, while the remaining patients had sporadic chelation or have not had deferoxamine treatment at all. Each patient underwent laboratory examinations and clinical cardiac evaluation with ECG and echocardiography.

## Results

Electrocardiography examinations showed cardiac dysrhythm occurring in two patients and 1<sup>st</sup> degree

heart block, 2<sup>nd</sup> degree heart block, and left ventricular hypertrophy (LVH), each occurring in one patient. The prevalence of cardiac dysfunction was 8%, with the mean of age was 12.7 (SD 7.7) years, and the mean of the serum ferritin was 4337.4 (SD 3755.1) ng/mL.

There were eight patients with systolic dysfunction, with shortening fraction below 28% and/or ejection fraction below 64%. Three patients (5%) had LV diastolic dysfunction and ten patients (16%) had RV diastolic dysfunction. From 21 patients, three had one or more abnormalities, two patients had LV and RV diastolic dysfunctions, and one had LV systolic and diastolic dysfunctions. Based on the operational definition used in this study, the prevalence of cardiac dysfunction by echocardiography examination was 29%, the mean age was 12.9 (SD 6.4) years, and the mean serum ferritin was 4074.6 (SD 2801) ng/mL.

The serum ferritin concentration correlated well with the cumulative blood volume transfusions ( $p=0.001$ ,  $r=0.408$ ) (**Figure 1**).

Four out of 62 patients were excluded from the analysis because they had never used DFO. Patients were then divided in to two groups. Group A with regular DFO (11 patients), mean ferritin level was 4163.2 (SD 2904.9) ng/ml. Group B (47 patients) with irregular DFO, mean ferritin level was 4255 (SD 3240.2) ng/mL There was a difference of ferritin level

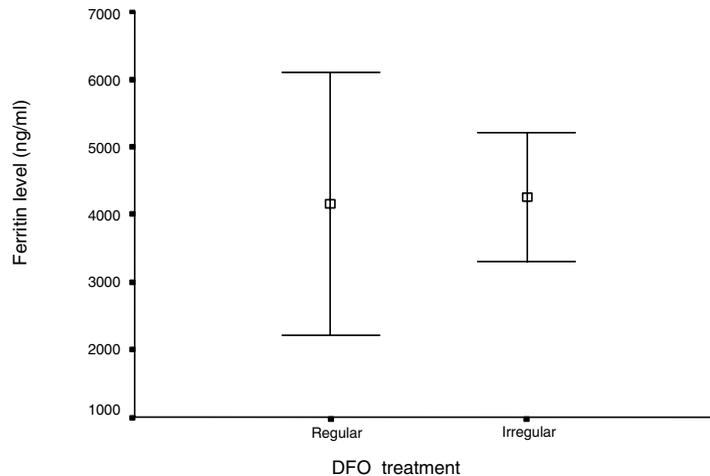


Figure 2. Correlation between serum ferritin with DFO treatment

between group A and B, but it was insignificant ( $p=0.472$ ) (Figure 2). Predictive value and cut off point of ferritin level in cardiac dysfunction could not be determined because the area under the ROC curve was only 53% ( $p=0.707$ ).

## Discussion

The amount of blood transfusion has not been proven to be an accurate index of iron overload, since iron turnover and iron absorption are increased and iron chelating therapy decreases the amount of deposited iron. The serum ferritin is highly correlated with the amount of iron deposited in tissue and is considered as a high sensitivity index.<sup>14</sup> In the present study, we found a good correlation between the amount of blood transfused and the ferritin level.

The negative correlation between ferritin level and DFO therapy may be due to a preexisting high level of ferritin or disproportionate DFO dose since its initial administration. The serum ferritin level is also influenced by ferritin release from damaged cells due to inflammation, infection, liver disorder or malignancy.<sup>2,15</sup> This study was not designed to determine these influencing factors.

Brittenham GM *et al*<sup>15</sup> concluded that early administration of DFO in proportional dose, effectively reduces the body iron burden and helps protect against complications and early death in patients with thalassemia major.

Cardiac complications are the most common cause of death in patients with  $\beta$ -thalassemia major. The most serious complications included arrhythmias, congestive heart failure, and pericarditis.<sup>17</sup> The pathophysiology of heart failure is unclear, although it is believed to be strongly related to the cardiac iron content and to the cumulative blood transfusion load. The three most frequent abnormal findings by ECG examination were left ventricular hypertrophy, dysrhythmia, and atrioventricular conduction delay (first and second degree of heart block). In this study, we found two dysrhythmia patients, one 1<sup>st</sup> degree heart block patient, one 2<sup>nd</sup> degree heart block patient, and also one left ventricular hypertrophy (LVH) patient.

The low prevalence of cardiac dysfunction by ECG examination (8%) in this study might be due to ECG insensitiveness in detecting cardiac dysfunction before the onset of clinically apparent disease.<sup>13</sup> Other possibility is that most subjects were in the young age group (<15 year old) leading to less possibility of cardiac involvement.

The prevalence of cardiac dysfunction by echocardiography was 29%, lower than the finding of Olivieri *et al* (37%)<sup>16</sup>; this may be due to the difference in the mean age of the subjects in this study which was 11.5 (SD 5.2) years, compared to 23 (SD 5) years in Olivier's study. The limitation of this study was that outpatients were included, while inpatients that might have severer symptoms of cardiac dysfunction were excluded.

Anemia, as a confounding factor in this study, could not be totally excluded, but we tried to minimize this factor by performing post transfusion echocardiography. The occurrence of cardiac disorder due to severe and progressive anemia is reversible.<sup>2</sup>

The negative correlation between ferritin level and cardiac dysfunction might be due to other causes such as myocarditis, which has a potential role in the development of congestive heart failure.

We concluded that there was no correlation between the serum ferritin levels with cardiac dysfunctions. Echocardiography examination was more sensitive than ECG in detecting cardiac dysfunction in thalassemic patient. Patients with serum ferritin level above 4000 ng/mL should undergo regular echocardiography examination to detect any possibility of cardiac dysfunctions.

### Acknowledgments

The authors wish to thank Mulyadi M Djer, MD and Syarif Rohimi, MD for their help in doing the echocardiography examinations.

### References

1. Spirito P, Lupi G, Melevendi C, Vecchio C. Restrictive diastolic abnormalities identified by Doppler echocardiography in patients with thalassemia major. *Circulation* 1990; 82:88-94.
2. Weatherall DJ, Clegg JB. The  $\beta$  thalassemyias. In: Weatherall DJ, Clegg JB, editors. *The thalassaemia syndromes*. 3<sup>rd</sup> ed. London: Blackwell scientific publications; 1981. p. 148-319.
3. Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. *Ann Intern Med* 1998;129:925-31.
4. Barton JC, McDonnell SM, Adam PC, Brissot P, Powell LW, Edwards CQ, et al. Management of hemochromatosis. *Ann Intern Med* 1998; 129:932-9.
5. McDonagh KT, Nenhuis AW. The thalassemyias. In: Nathan DG, Oski FA, editors. *Hematology of infancy and childhood*. 4<sup>th</sup> ed. Philadelphia: WB Saunders; 1993. p. 783-857.
6. Worwood M. Pathogenesis and management of haemochromatosis. *Br J Haematol* 1999;105: 16-8.
7. Lau KC, Li AMC, Hui PW, Yeung CY. Left ventricular function in  $\beta$  thalassaemia major. *Arch Dis Child* 1989; 64:1046-51.
8. Edwards CQ, Kushner JP. Screening for hemochromatosis. *N Engl J Med* 1993; 328:1616-20.
9. Pippard NE. Iron loading and chelation therapy. In: Weatherall DJ, editor. *The thalassemyias*. New York: Churchill Livingstone; 1983. p. 103-13.
10. Garcia P. Iron in today's laboratory. *Clin Biochemist Rev* 1997; 18:113-7.
11. Ehlers KH, Giardina PJ, Lesser ML, Engle MA, Hilgartner MW. Prolonged survival in patients with beta-thalassaemia major treated with deferoxamine. *J Pediatr* 1991; 118:540-5.
12. Kremastinos DT, Tsiapras DP, Tsetsos GA, Rentoukas EI, Vretou HP, Toutouzas PK. Left ventricular diastolic Doppler characteristics in  $\beta$ -thalassaemia major. *Circulation* 1993; 88:1127-35.
13. Leon MB, Borer JS, Bacharach SL, Green MV, Benz EJ, Griffith P, et al. Detection of early cardiac dysfunction in patients with severe beta-thalassaemia and chronic iron overload. *N Engl J Med* 1979; 22:1143-8.
14. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassaemia. *Blood* 1997; 89:739-54.
15. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucher EE, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassaemia major. *N Engl J Med* 1994; 331:567-73.
16. Olivieri NF, Nathan DG, Mac Millan JH, Wayne AS, Liu AP, McGee A, et al. Survival in medically treated patients with homozygous  $\beta$ -thalassaemia. *N Engl J Med* 1994; 331:574-8.
17. Kremastinos DT, Tiniakos G, Theodorakis GN, Katritsis DG, Toutouzas PK. *Circulation* 1995; 91:66-71.
18. Koren A, Garty itzhak, Antonelli D, Katzumi E. Right ventricular cardiac dysfunction. *Am J Dis Child* 1987; 141:93-6.