Original Article

Relationship between Serum Ferritin Level and Left Ventricular Function in Thalassemia Patients

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Abstract:

Objective: *The study aim was to investigate the relationship between serum ferritin levels and left ventrivular ejection fraction (LVEF) among thalassemia patients.* ***Materials and Methods:*** *Adult thalassemia patients at Panyananthaphikkhu Chonprathan Medical Center and Faculty of Medicine Vajira Hospital from May 6, 2014 to October 26, 2015 were enrolled. Clinical parameters and outcome data were extracted from medical records. Two-dimensional (2D) echocardiography and serum ferritin were performed within 2 weeks. If the echocardiography result showed structural heart disease, we excluded the patient from this study.* ***Results:*** *Thirty-five thalassemia patients were examined (female 21 and male 14). Twenty were transfusion dependent thalassemia (TDT), while 15 were nontransfusion dependent thalassemia (NTDT). Mean age was 41.5 years old. History of blood transfusion was 85.7%. Mean amount of blood transfusion was 22 units. The mean hematocrit was 22.87%. The median serum ferritin level was 1,201 ng/mL. Median serum ferritin level among males was higher than among females, but the difference was insignificant. The mean ejection fraction was 65%. Serum ferritin levels showed a weak negative correlation with the LVEF.* ***Conclusion:*** *Our results revealed serum ferritin levels showed a negative correlation with the left ventricular ejection fraction.*

Keywords : ● *Echocardiography* ● *Left ventricular ejection fraction* ● *Serum ferritin* ● *Thalassemia*

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นิพนธ์ต้นฉบับ

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บทคัดย่อ

วัตถุประสงค์ *เพื่อศึกษาความสัมพันธ์ระหว่างค่า serum ferritin และ left ventricular ejection fraction (LVEF) ในผู้ป่วยธาลัสซีเมียในปริมาณที่แตกต่างกันมีผลต่อการทำงานของหัวใจ* ***วัสดุและวิธีการ*** *ผู้ป่วยธาลัสซีเมียอายุมากกว่า 18 ปีขึ้นไป ตั้งแต่ 6 พฤษภาคม พ.ศ. 2557 ถึง 26 ตุลาคม พ.ศ. 2558 โดยเก็บข้อมูลพื้นฐานทางคลินิกข้อมูลพื้นฐานทางห้องปฏิบัติการการรักษารวมถึงผล ferritin และผลการตรวจหัวใจด้วยคลื่นความถี่สูงในระยะเวลาห่างกันไม่เกิน 2 สัปดาห์ หากผลการตรวจหัวใจด้วยคลื่นความถี่สูงมีความผิดปกติจากโรคหัวใจแต่กำเนิด จะตัดผู้ป่วยรายนั้นออกจากการศึกษา* ***ผลการวิจัย*** *มีผู้ป่วยธาลัสซีเมียในการศึกษาทั้งหมด 35 ราย (หญิง 21 ราย ชาย 14 ราย) โดยมีชนิดพึ่งพาเลือด 20 รายและชนิดไม่พึ่งพาเลือด 15 รายค่าเฉลี่ยของอายุเท่ากับ 41.49 ปี ผู้ป่วยมีประวัติ*

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รับเลือดร้อยละ 85.7 ค่าเฉลี่ยจำนวนเลือดแดงที่ใช้เท่ากับ 22 ยูนิต ผล Hematocrit เฉลี่ยเท่ากับร้อยละ 22.87 ค่ามัธยฐาน serum ferritin เท่ากับ 1,201 ng/mL ค่ามัธยฐาน serum ferritin ในเพศชายสูงกว่าเพศหญิงเล็กน้อยแต่ไม่มีความแตกต่างกันทางนัยสถิติ ค่ามัธยฐานของ LVEF เท่ากับร้อยละ 65 serum ferritin มีความสัมพันธ์เชิงผกผันกับ LVEF อย่างไม่มีนัยสำคัญทางสถิติ ***สรุป*** *Serum ferritin ที่สูงขึ้นมีความสัมพันธ์กับ LVEF ที่ต่ำลงในผู้ป่วยธาลัสซีเมียอย่างไม่มีนัยสำคัญทางสถิติ*

คำสำคัญ : ● *Echocardiography* ● *Left ventricular ejection fraction* ● *Serum ferritin* ● *Thalassemia*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2559;26:207-13.

Introduction

Thalassemia syndrome and hemoglobinopathies are common and clinically diverse in Thailand. The prevalence of thalassemia in Thailand is about 1%, approximately 65,000 people.[1] Almost all are severe thalassemia patients receiving regular blood transfusions and eventually developing organ damage from iron overload. Iron overload is a continuous and more significant complication in thalassemia.[2]

The main causes of iron overload in transfusion dependent thalassemia (TDT) are blood transfusion therapy and increased gastrointestinal tract absorption.[3] Most concern is end organ damage from iron overload especially cardiac complication. Iron loading of cardiac tissue is often a late and hazardous complication of iron overload. TDT, in the absence of iron chelation therapy, develops progressive iron accumulation, which is responsible for tissue damage and increases the mortality rate.[4] Assessments include indirect cardiac iron assessment such as serum ferritin, electrocardiogram and echocardiography as well as the direct method and invasive assessment such as myocardial biopsy and liver biopsy.[5] Measurement serum ferritin and monitoring of LVEF are easy to perform tests, widely used, and available in most public hospitals. Serum ferritin is well established, and usually correlated with iron stores and prognostically related in thalassemia major.[3] LVEF can be quantified using MRI, MUGA scan (Multiple Gated Acquisition scan) or echocardiography. The first two methods have advantages over echocardiography due to being less operator-dependent.[3] Thus, we studied the association of serum ferritin and LVEF among thalassemia patients.

Materials and Methods

Cross-sectional data was collected between May 6, 2014 and October 26, 2015 at the Hematology Clinic at Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University and Vajira Hospital, Navamindradhiraj University, Thailand.

Data were gathered through interviews, clinical examinations, demographic characteristics, treatment type, biochemical variables and the ejection fraction of 35 thalassemia patients. The inclusion criteria included patients diagnosed with thalassemia and age 18 years and above. The exclusion criteria comprised patients with hepatitis, porphyria, thyroid disease, diabetes mellitus, autoimmune disease, malignancy, chronic inflammation or infection. Cardiac evaluation of all patients was performed after serum ferritin measurement within two weeks. 2D-echocardiography (GE, VIVID E9) was performed by cardiologists. When the echocardiography result showed structural heart disease, we excluded the patient from this study. Complete blood count was performed by Sysmex XN-3000 automate hematology analyzer. Hemoglobin typing was performed using the capillary electrophoresis method. All patients provided written informed consent. The study was approved by the Institutional Review Board of Chonprathan Hospital and Vajira Institutional Review Board.

Descriptive statistics were calculated for all variables, including median and QIR, 25th and 75th percentiles for continuous factors. For categorical variables, frequencies and percentages were estimated. The Kruskal-Wallis test was used to assess any significant differences in terms of continuous relation between any of the eight subject group (Diagnosis groups). The Mann-Whitney

U test was compared between two groups. Fisher's exact test and logistic regression test were used for categorical factors. Univariate distribution relationships between LVEF and serum ferritin were assessed by Pearson's correlation analysis. Multivariate relationship by partial correlation analysis was used to assess whether the addition of any clinical characteristics improved the prediction of the presence of significant LVEF. All analyses were performed using SPSS version 21.0; A 2-sided probability value of < 0.05 was considered statistically significant.

Results

A total of 35 thalassemia patients were included. Mean age was 41.5 years old. Sixty percent of them were female (Table 1). Most of our patients received blood transfusions. The mean unit of packed red blood cell was 22. Median serum ferritin level was 1,201 ng/mL (IQR: 656, 1990). Ferritin levels were lower than 1,000 ng/mL among 17 patients and above 1,000 ng/mL among 18 patients (Table 2). Mean ferritin among males was higher than females, but the difference was insignificant ($p = 0.687$).

The range of LVEF was 59% to 89% and the median was 65%. Mean ejection fractions among males and females were 67.53% and 67.15%, respectively. However, no significant difference was found ($p = 0.896$).

Serum ferritin showed a negative correlation with left ventricular ejection fraction (r = -0.122 and $p = 0.485$). Serum ferritin levels showed a weak negative correlation (r = -0.122; $p = 0.485$) with the left ventricular ejection fraction (Figure 1).

Then comparisons were made between alpha thalassemia, beta thalassemia, and alpha & beta-thalassemia. We found the mean of hematocrit level among patients with beta thalassemia was significantly lower than that for patients with alpha thalassemia and alpha & beta-thalassemia ($p = 0.039$). Mean ferritin and LVEF did not

Table 1 Demographic data

Variables	N (%) or Mean ± SD
Sex	
Male	14 (40)
Female	21 (60)
Age (yr.)	41.49 ± 16.35
Type of thalassemia	
HbE/β thalassemia	11 (31.14)
AE Bart's	4 (11.4)
HbH-CS	4 (11.4)
HbH	4 (11.14)
Unknown type	3 (8.6)
EF Bart's	2 (5.7)
Beta thalassemia	2 (5.7)
Homozygous HbCS	1 (2.9)

Table 2 Clinical characteristic data of 35 patients

Variables	N (%) or Mean ± SD	Median (Q_1, Q_3)
History of blood transfusion	30 (85.7)	
Unit of blood transfusion	22 ± 40.95*	9 (3, 20)
Hb (g/dL)	6.92 ± 1.52	6.6 (5.8, 7.8)
Less than 7	22 (62.9)	
More than 7	13 (37.1)	
Hct (%)	22.87 ± 5.22	22 (19.71, 26.7)
Ferritin (ng/mL)	2,388.44 ± 5,085*	1,201 (656, 1990)
Less than 1,000	17 (48.6)	
More than 1,000	18 (51.4)	
LVEF(%)	67.3 ± 8.29	65 (60.67, 73.74)
Less than 60	8 (22.9)	
More than 60	27 (77.1)	

* Non normal distribution.

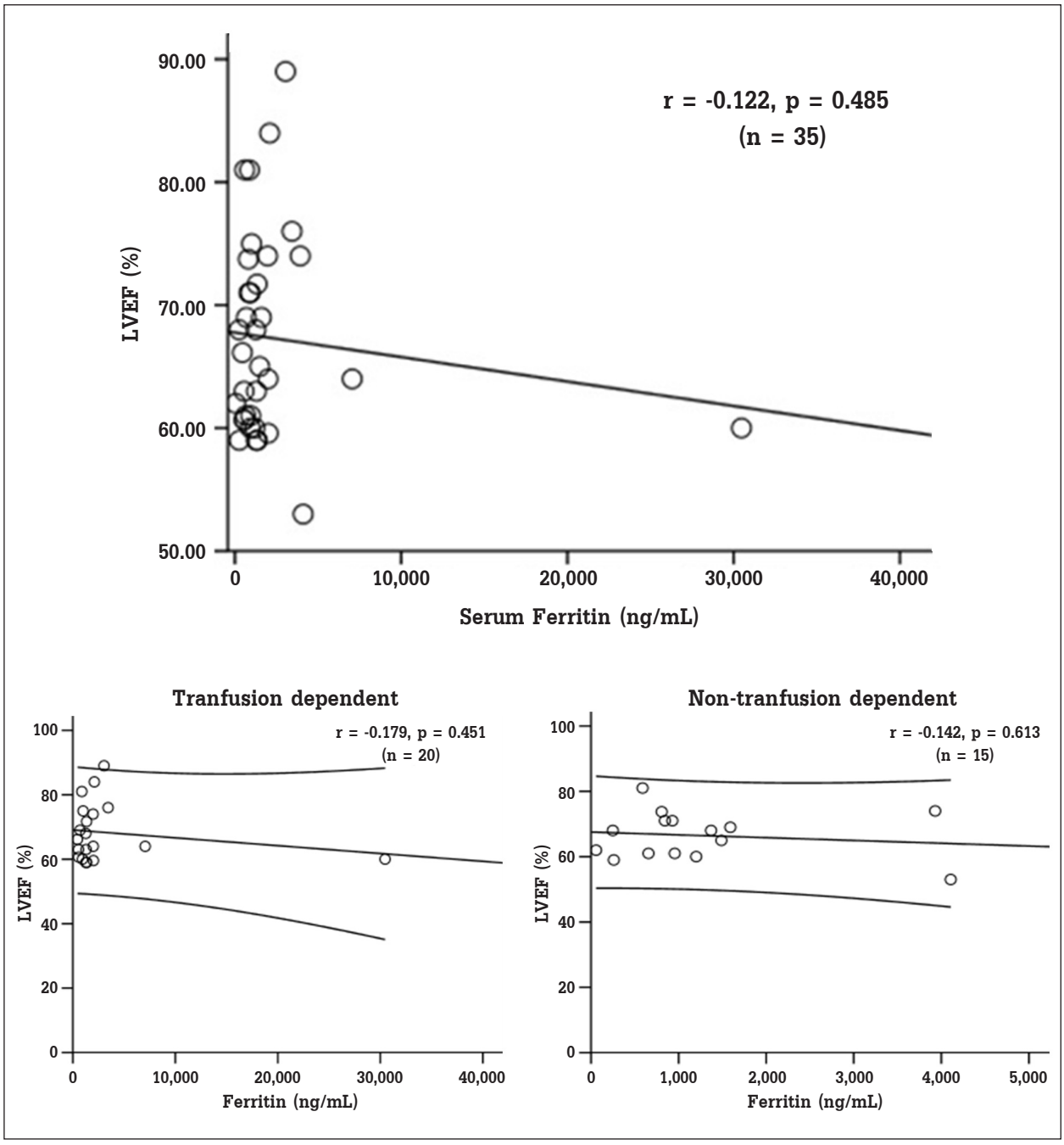

Figure 1 Left ventricular ejection fraction (LVEF) and Ferritin correlation

differ significantly in three groups (p = 0.776), (p = 0.577). Based on their clinical severity and transfusion requirement, we classified cases phenotypically in two main groups: 1) transfusion dependent thalassemia (TDT) and 2) nontransfusion dependent thalassemia (NTDT). Approximately 60% were TDT. Mean ferritin and LVEF didnot differ significantly in the two groups (p = 0.755), (p = 0.516) (Table 3). Serum ferritin levels showed a weak negative correlation (r = -0.179; p = 0.451) with the left ventricular ejection fraction found in the TDT group (Figure 1). The type of iron chelation therapy did not significantly affect the serum ferritin level in the two groups (p = 0.307) (Table 3).

Discussion

In recent years, many methods have been used to measure serum iron level. Measurement of serum ferritin, having no inflammatory disorders or hepatic involvement, is an indirect method.[6] To assess of iron overload of the body, serum ferritin is the most commonly

Table 3 Demographic and laboratory characteristics of TDT and NTDT

		Transfusion dependent		p-value
		No (n = 15)	Yes (n = 20)	
Sex	F	5 (33.3%)	15 (75%)	0.014*
	M	10 (66.7%)	5 (25%)	
Age (years)		37.07 ± 14.81	44.8 ± 17.02	0.169
Weight (kg)		50.21 ± 7.78	52.27 ± 19.11	0.697
Height (cm)		161.4 ± 8.08	153.45 ± 30.67	0.336
BMI (kg/m^2)		19.23 ± 2.32	19.9 ± 4.31	0.588
ECOG	0	15 (100%)	16 (80%)	0.119
	1	0 (0%)	4 (20%)	
History of blood transfusion	No	4 (26.7%)	1 (5%)	0.141
	Yes	11 (73.3%)	19 (95%)	
History of splenectomy	No	13 (86.7%)	15 (75%)	0.672
	Yes	2 (13.3%)	5 (25%)	
Hb (g/dL)		7.74 ± 1.83	6.38 ± 0.86	0.016*
Hct (%)		25.67 ± 5.97	21 ± 3.32	0.013*
LVEF (%)		66.45 ± 7.24	68.31 ± 8.97	0.516
Ferritin (ng/mL)		928.1	1,314	
Median (IQR)		(589, 1489)	(905.4, 2048)	0.755
Type of iron chelation				
Deferoxamine		0	2 (12.5%)	0.307
Deferasirox		0	1 (6.3%)	
Deferiprone		6 (85.7%)	13 (81.2%)	
Deferoxamine + Deferiprone		1 (14.3%)	0	

Values presented as n (%) and mean ± SD, p-value corresponds to Fisher's exact test and Independent t-test.

employed test, as it is simple, cost effectiveness and generally available.[7] The serum ferritin level has been commonly used as a predictor of iron overload.[8] A serum ferritin level more than 1,800 ng/mL is associated with an elevated cardiac iron concentration, and a level more than 2,500 ng/mL is associated with an increase in the prevalence of cardiac events.[9]

Echocardiography is useful to study structural changes of the heart. Echocardiography is the main method used in screening iron overload conditions for heart disease as part of the initial and regular follow-up evaluations.[10] While echocardiography is a beneficial tool for cardiac function monitoring in clinical practice, several studies have proved that it is not sensitive enough for early detection of the preclinical stage of cardiac involvement among thalassemia major patients due to the typically late onset of signs and symptoms.[11]

In the present study, we measured serum ferritin and also used echocardiography among 35 thalassemia patients. Median ferritin was 1,201 ng/mL (IQR: 656, 1990). Mean LVEF was 65%. Mean ferritin and LVEF in TDT compared with NTDT showed no significant difference.Mean ferritin and LVEF did not differ between the two groups probably due to iron chelation therapy in TDT.

Our study showed a negative correlation between LVEF and serum ferritin. Another study showed that serum ferritin level did not significantly correlate with

ejection fraction among patients.[12] We found no significant correlation between LVEF and serum ferritin level, but a larger population might have shown significance. Bosi and colleagues revealed a large population of β-thalassemia patients following an adequate transfusion and chelation therapy in which serum ferritin showed a weak negative correlation with LVEF.[13] Ashena et al. did not find any definite significant relationship between serum ferritin concentration and systolic and diastolic indices.[14]

Several studies have shown that serum ferritin is a useful marker to predict cardiac function, but our result was differed and could be justified by the reasons stated below.

1. Serum ferritin is raised in any kind of inflammation. Measuring serum ferritin level at the time of infection or inflammation affects the result of the study.

2. Serum ferritin concentration changes due to deferoxamine injections. Patients' concentrations change because regularly receiving these injections in a week temporary increases the amount of serum ferritin (see in Figure 1, serum ferritin 30,467 ng/mL). Serial serum ferritin will predict a better clinical correlation.

3. Serum iron uses a long time to gradually accumulate in body organs, including the heart, and a time gap is noted between process start and finding measurable changes in the heart. Consequently, a single level measure of serum ferritin will not specify the true amount of body iron stores. We should measure serum ferritin concentration at regular intervals and then assess the relation between mean ferritin level and mean LVEF.

4. The study included a suboptimal number of patients (n = 35). A larger number of patients are needed to appropriately assess the relation between serum ferritin concentration and LVEF. To proceed, conducting are search study with a larger number of patients may be able to reveal a significant relationship between serum ferritin concentration and LVEF.

5. The mix of thalassemia patients between NTDT and TDT, cardiac siderosis and subsequent cardiac disease did not seem to be a major concern in the NTDT group.[15-18] Therefore, we suggest future studies should especially investigate the TDT group.

6. Measuring the surrogate outcomes, such as cardiac magnetic resonance T2* should be performed to evaluate cardiac siderosis.

Clinical application of this study included maintaining an awareness when testing for ferritin among patients with a condition, e.g., infection or inflammatory processes, collagen diseases, hepatic diseases, and malignancy.[19] Evidence has indicated that increased serum ferritin levels might be a defense mechanism of the body against oxidative stress.[20] The most common causes of non-iron overload hyperferritinemia include nonalcoholic fatty liver disease (NAFLD), alcohol ingestion, sepsis, malignancy and autoimmunity. Other rare causes of hyperferritinemia include hereditary hyperferritinemia-cataract syndrome, porphyria cutanea tarda and aceruloplasminemia.[19]

Clinical practice guidelines to diagnose and manage thalassemia syndromes suggest TDT patients with iron overload and serum ferritin more than 1,000 ng/mL on two occasions at least two weeks apart should receive iron chelation therapy. NTDT patients with serum ferritin over 800 ng/mL and/or liver iron concentration over 5 mgFe/g dry weight should receive iron chelation therapy.[21]

Summary

It appears that no significant relation of serum ferritin and LVEF could be observed among thalassemia patients. Several studies have shown that serum ferritin is a useful marker to predict cardiac function but this study was limited by the small sample size (n = 35), a mixed population between NTDT and TDT, iron chelation therapy and the use of spot ferritin. Hopefully, larger samples and longitudinal studies among patients with TDT could give more conclusive results.

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