Correlation of Serum Ferritin and Liver Enzymes in Thalassemia Major Children

Aklima Akter[1*]

Abstract

Background: Worldwide, thalassemia is the most prevalent gene defect. The main treatment of thalassemia is the blood transfusion along with chelation therapy. Repeated blood transfusions leads to iron overload along with chelation therapy detoriates liver function. This study aims to see the correlation between liver enzymes with serum ferritin in children with β-thalassemia major.

Materials and methods: From Chattogram Medical College Hospital 79 children suffering from thalassemia major in the age group of 5-12 years who received regular blood transfusions and iron chelators were included in this cross sectional study. Serum ferritin and liver enzymes [Alanine Transaminase (ALT) Aspartate Transaminases (AST) Alkaline Phosphatase (ALP) and Gamma Glutamyltransfarase (GGT)] were tested and their correlation was assessed. Pearson sbivariate correlation coefficient was used to determine the correlation.

Results: The mean age was 8.5±2.4 years and 57% were male. The mean age at diagnosis of thalassemia was 10.7±4.2 months and mean number of transfusion was90±29 and ranged between 40-140 transfusions. All of the children were on oral ironchelation therapy and the average age of initiation chelation therapy was 5.7±1.1years. Sixty-four (81%) children had growth retardation. Mean serum ferritin level was 3740.7±2184.8ng/ml and only 3.8% of the patients had serum ferritin level <1000 ng/ml. The mean level of serum ALT, AST, ALP, and GGT was 121.9±73.9, 89.9±49.1, 256.0±114.9 and 52.8±35.8IU/L, respectively. Respectively, 57(72.2%, 65(82.3%), 19(24.1%) and 23(29.1%) patientshad elevated ALT, AST, ALP and GGT levels. Serum ferritin had a positive correlation with ALT ($r=0.639$, $p<0.001$), AST ($r=0.659$, $p<0.001$), ALP ($r=0.535$, $p<0.001$), GGT ($r=0.535$, $p<0.001$) total number of transfusion received ($r=0.539$, $p<0.001$). Age of starting iron chelation therapy was positively correlated between and serum ferritin and liver enzyme levels ($p<0.05$).

Conclusions: In thalassemia major patients liver enzymes are raised and positively correlated serum ferritin. Regular monitoring of liver functions is necessary to see early onset of hepatic dysfunction.

1. Assistant Professor of Biochemistry
Marine City Medical College, Chattogram.

***Correspondence: Dr. Aklima Akter**
Cell : 01674 46 36 48
E-mail: draklimaa@gmail.com

Submitted on : 11.03.2025
Accepted on : 05.05.2025

Key words: Liver enzymes; Serum ferritin; Transfusion dependent thalassemia.

Introduction

Worldwide thalassemia is a common genetic disorder. In thalassemia there is deficiency of beta globin chain production resulting in ineffective erythropoiesis causing lack of affinity of circulating hemoglobin F to 2,3 diphosphoglycerate.[1] Repeated blood transfusion is the main treatment which prevents growth retardation, causes skeletal changes due to expansion of bone marrow and development of masses from extra medullary heamatopoiesis.[2] Regular monitoring and management is required for repeated blood transfusion causing iron overload through long term iron chelation therapy. Inadequate chelation therapy leads to cardiac arrhythmia, cardiomyopathy and heart failure causing death, meanwhile liver diseases and endocrine diseases increases the rate of mortality and morbidity.[3] Liver acts as the primary site of iron deposition in transfusion dependent children and liver injury is the main reason of morbidity. Iron overload is visible in both hepatocytes and reticulo endothelial cells. Liver injury due to iron overload is characterized by fibrosis which ultimately leads to liver cirrhosis.[4] Liver remains as the primary site for ferritin and transferrin synthesis and for iron storage. Normally in liver iron is protein bound and free ferrous iron is toxic. Protein free iron increases the production of free radicals which is seen in lipid peroxidation and in hepatotoxicity.[5] Previous studies reflected good correlation between serum ferritin and hepatic iron concentration.[6]

In Bangladesh earlier studies revealed that in thalassemia children the level of serum ferritin bilirubin, alanine transaminase, aspartate transaminase and alkaline phosphatase increases than in healthy children. Previous studies found statistical significance between iron overload and jaundice in thalassemia children.[7] Previous studies from Bangladesh showed correlations between serum ferritin and liver enzymes but the results were inconsistent. Some studies showed statistically

significant positive correlations, whereas some studies revealed insignificant or weak positive correlations.[8,9] The effect of iron chelation therapy on liver enzymes showed inconsistent result in earlier studies.[10,11] Moreover, there is a scarcity of data regarding the correlation between iron overload and liver damage in thalassemia patients. Therefore, the present study aimed to analyze the level of serum ferritin and liver enzymes and to develop the possible correlation between the serum ferritin concentrations and the level of liver enzymes in β-thalassemia major patients receiving treatment in a tertiary hospital in Chattogram, Bangladesh.

Materials and methods

This cross sectional study was done in Department of Biochemistry and pediatrics' of Chittagong Medical College Hospital. 79 diagnosed cases of thalassemia major were included in the study by convenience sampling. Patients who received blood transfusion in last 15 days and with chronic diseases like tuberculosis, hepatitis B, HbE beta thalassemia and malignancy were discarded from the study. Before start the study necessary permission was taken from proper authorities.

Results

Table I Age and gender of the patients (n=79)

Variables	Frequency	Percentage (%)
Age		
5 years	11	13.9
6 years	09	11.3
7 years	09	11.3
8 years	11	13.9
9 years	10	12.6
10 years	08	10.1
11 years	10	12.6
12 years	11	13.9
Mean age	8.5+2.4	
Gender		
Male	45	56.9
Female	34	43.0
Age at diagnosis		
Median (Range)	10.7+4.2	
<12 months	48	60.8
≥12 months	31	39.2

The study revealed that bulk 11(13.9%) of the patients were in age of 5 years and 12 years. Among the patients 45(56.9%) were males. The earliest age at diagnosis was 4 months in the study but in 39.2% of the cases diagnosis was made beyond one year of age. The mean age at diagnosis was 10.7±4.2 months (Table I).

Table II Relation between age with number of transfusion required and serum ferritin level

Age group	No. of transfusion required (Mean ± SD)	Serum ferritin level (Mean±SD)
5-7 years (29)	61.48+12.9	2748.14 ±1741.7
8-10 years(29)	95.39+15.45	3574.17±2002.5
11-12 years (21)	125.52+14.13	5041.24±2144.0
p value	0.001	0.001

*F test (Analysis of variance).

The study showed that number of transfusion was higher in 12 years of children and significant association ($p<0.005$) between serum ferritin and age group indicating that as age was increased, the serum ferritin level was also increased.

Table III Correlation between age and serum ferritin level

Age group	Serum ferritin level (Mean±SD)	p value
5-7 years (29)	2748.14 ±1741.7	0.001
8-10 years (29)	3574.17±2002.5	
11-12 years (21)	5.41.24±2144.0	

*F test (Analysis of variance).

Table III showed a positive correlation between serum ferritin and age group indicating that increase the age was associated with higher level of serum ferritin.

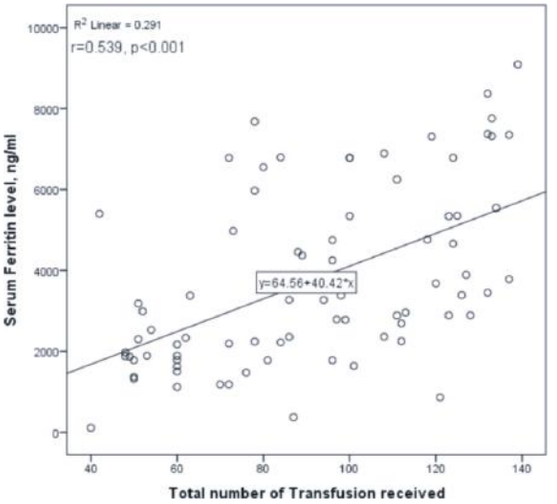

Figure 1 Scatter and dot plot showing correlation and regression line between total number of transfusion received and serum ferritin

The figure showed a significant positive correlation between total number of transfusion received and serum ferritin level (Pearson correlation r=0.539, p<0.001).

Table IV Correlation between starting age of iron chelation therapy and serum ferritin and liver enzymes

Biochemical parameters	Pearson correlation coefficient (r)	p value
Serum ferritin, ng/ml	0.310	0.005
Serum ALT, IU/l	0.399	<0.001
Serum AST, IU/l	0.350	0.002
Serum ALP, IU/L	0.303	0.007
Serum GGT, IU/L	0.262	0.020

Table IV shows a weak positive correlation between age of starting iron chelation therapy and serum ferritin and liver enzyme levels, indicating that delayed initiation of iron chelation therapy was associated with higher level of serum ferritin and liver enzymes.

Table V Relation between growth retardation and serum ferritin and liver enzymes

Biochemical paramters	Growth retardation		p value*
	Absent (n=15)	Present (n=64)	
Serum ferritin, ng/ml	2486.3±1914.1	4043.5±2152.3	0.013
Serum ALT, IU/l	73.7±60.7	133.2±72.4	0.004
Serum AST, IU/l	63.5±40.5	96.0±49.1	0.020
Serum ALP, IU/L	197.7±80.1	269.7±117	0.028
Serum GGT, IU/L	32.3±26.3	57.6±34.7	0.013

*Independent sample 't' test.

The mean serum ferritin and liver enzyme levels were significantly higher among children with growth retardation than the children with normal growth pattern (p<0.05).

Discussion

The current study was done to to investigate the liver enzymes in relation to serum ferritin level in children with β-thalassemia major patients attending in Chittagong Medical College and Hospital, Bangladesh. The present study showed a positive correlation between serum ferritin and ALT, AST, ALP, and GGT levels. Thalassemic children of 5 to 12years ofage were included in the study. The meanage of the studied patients was 8.5±2.4. Male represented 57% of cases and females were 4f 3%, with a male female ratio of 1.3:1. The male to female ratio observed in the present study was also consistent with the values reported in previous studies carried out in Bangladesh.[12] In a previous study, foundthat, 1% β Thalassemia major children was diagnosed at less than 2 year of their age. In the current study, the mean age at diagnosis was 10.7±4.2 months, the earliest age at diagnosis was 4 months but in 39.2% of the cases diagnosis was made beyond one year of age.[13] All thalassemic patients of this study were on oral iron chelation therapy. The average age of initiation of chelation therapy was 5.7±1.1 years and the the average duration of chelation therapy was 4.8±1.1 years. Thalassemia International Federation guideline recommends that chelation therapy is initiated when serum ferritin levels reach ≥1000 ng/ml, which usuallyoccurs after the first 10–20 transfusions or around 2–3 years ofage.[14] In the current study majority cases were in the age group 5–7 years atthe time of initiation of chelating agent therapy, which shows that initiation of chelation therapy in the study center started at much later ages compared with the optimal age recommended by the Guidelines. In the current study, the average serum ferritin level(3740.7±2184.8 ng/ml) was considerably higher than its peak value (1000 ng/mL),showing that regularly transfused patients were in iron overload status, which shows iron levels and serum ferritin have a positive correlation. The mean serum ferritin level was 3278.64 ng/ml with the lowestof 285.2 ng/mL and the highest of 10940.2 ng/ml in 138 TDT children in the study of Moshary which revealed iron overload is mainly from blood transfusions and to alesser extent from increased gastrointestinal absorption which is the major cause of morbidity and mortality intransfused thalassemia patients.[15] The mean level of serum ALT, AST, ALP, and GGT was 121.9±73.9,89.9±49.1,256.0±114.9 and 52.8±35.8 IU/L, respectively, in the present study. The proportion of patients with elevated ALT, AST, ALP and GGT levels were 72.2%, 82.3%, 24.1% and 29.1%, respectively. A study from Bangladesh observed that serum AST, ALT, and ALP levels were much higher in β-thalassemia patient than in normal children.[16] In the present study the liver enzymes ALT, AST, ALP and GGT had a positive correlation with serum ferritin level, which coincides with another study, where a positive correlation is seen between serum ferritin and ALT, AST and ALP.[15] These positive correlations between serum ferritin and hepatic

enzymes shows that high serum ferritin levels in beta-thalassemia leads tohepatic dysfunction. As a result liver functions should be monitored at regular intervals in patients with beta-thalassemia major. However, few studies failed to demonstrate any significant relationship between serum ferritin and liver function in thalassemia major.[17] There was a positive correlation between total number of transfusion received and serum ferritin level in the current study. In another study it was seen that as soon as the serum ferritin level crosses the value of 1000ng/ml and numberof transfusions are more than 30, liver enzymes starts to increase.[18] Present study indicated that, abnormal liver function was evident at earlier age in children with β-thalassemia major patients. These abnormalities in the present study stresses the need for further evaluation and improvement in the management of thalassemia patients in Bangladesh. The reasons are probably multiple transfusions, lower pre-transfusion hemoglobin level and inadequate chelation therapy, and severeanemia. Iron overload may cause liver injury. This is reflected by significant elevation of serum; ALT and AST activities and elevated serum ferritin level in transfusion dependent β-thalassemia major patients. Present study findings suggest that monitoring of AST, ALT and albumin levels is important because they may reflect the severity of liver iron overload. Findings of the present study and the existing evidences findings highlight the importance of prevention measures and timely diagnosis and management of iron over load in β-thalassemia major patient.

Limitation

Single centre study and study desing is cross sectional, so the study might not accurately reflect the whole population of Bangladesh.

Conclusion

From present study it is concluded that children with beta-thalassemia had hepatic dysfunctions in the form of abnormal liver enzymes and this occurring as soon serum ferritin level crosses as 1000 ng/ml and becomes highly significant after the serum ferritin levels of 3000 ng/ml. There was a positive correlation between serum ferritin with liver enzymes and number of transfusion. Due to potential toxic effect of iron overload in hepatocytes there is delayed initiation of iron chelation therapy was associated with higher level of ferritin and liver enzyme. These results Support the need for vigilant clinical evaluation of growth, as well as liver function evaluation in beta-thalassemia major Children.

Recommendation

Based on the study findings, it could be recommended that blood transfusion and serum ferritin level should be carefully monitored in patients with β-thalassemia major. Future prospective studies should be conducted to evaluate the effect of early and adequate chelation therapy on children with β-thalassemia major.

Acknowledgement

The author express their gratitude to the authorities of

- Chittagong Medical College Hospital
- Department of Biochemistry, CMCH
- Department of Pediatrics, CMCH.

Contribution of author

The whole study was solely conducted by the author herself.

Disclosure

The author declared no conflict of interest.

References

1. Risoluti R, Materazzi S, Sorrentino F, Bozzi C, Caprari P. Update on thalassemia diagnosis: new insights and methods. Talanta. 2018;183:216-222.

2. Galanello R, Origa R. Beta-thalassemia. Orphanet journal of rare diseases. 2010;5(1):1-5.

3. Taher AT, Musallam KM. Inati A. Iron overload: consequences, assessment, and monitoring. Hemoglobin. 2009;33(sup1):S46-57.

4. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology 2014, the American Society of Hematology Education Program Book. 2017;(1):265-271.

5. Sobhani S, Rahmani F, Rahmani M, Askari M, Kompani F. Serum ferritin levels and irregular use of iron chelators predict liver iron load in patients with major beta thalassemia: a cross-sectional study. Croat Med J. 2019 ;60:405-413.

6. Angulo IL, Covas DT, Carneiro AA, Baffa O, Elias Junior J, Vilela G. Determination of iron-over load in thalassemia by hepatic MRI and ferritin. Revista Brasileirade Hematologiae Hemoterapia. 2008;30:449-452.

7. Sultana N, Sadiya S, Rahman MH. Correlation between serum bilirubin and serum ferritin level in thalassaemia patients. Bangladesh Journal of Medical Biochemistry. 2011;4(2):6-12.

8. Al-Moshary M, Imtiaz N, Al-Mussaed E, Khan A, Ahmad S, Albqami S. Clinical and biochemical assessment of liver function test and its correlation with serum ferritin levels in transfusion-dependent thalassemia patients. Cureus. 2020;12(4): e7574.

9. Asif M, Manzoor Z, Farooq MS, Kanwal A, Shaheen U, Munawar SH et al. Correlation between serum ferritin level and liver function tests in thalassemic patients receiving multiple blood transfusions. International Journal International Journal of Research in Medical Sciences. 2014;2(3):988-1002.

10. Hashemizadeh H, Noori R. Assessment hepatomegaly and liver enzymes in 100 patients with beta thalassemia major in Mashhad, Iran. Iranian journal of pediatric hematology and oncology. 2012;2(4):171.

11. Soliman A, Yassin M, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, De Sanctis V. Longitudinal study on liver functions in patients with thalassemia major before and after deferasirox (DFX) therapy. Mediterranean Journal of Hematology and Infectious diseases. 2014;6(1):1-5.

12. Hossain MS, Raheem E, Sultana TA, Ferdous S, Nahar N, Islam S, et al. Thalassemias in South Asia: Clinical lessons learnt from Bangladesh. Orphanet journal of rare diseases. 2017;12(1):1-9.

13. Tahura S. Thalassemia and other Hemoglobinopathies in Bangladeshi children. Imp J Interdiscip Res. 2017;3:180-184.

14. Pinto VM, Forni GL. Management of iron overload in beta-thalassemia patients: Clinical practice update based on case series. International Journal of Molecular Sciences. 2020;21(22):8771.

15. Al-Moshary M, Imtiaz N, Al-Mussaed E, Khan A, Ahmad S, Albqami S. Clinical and biochemical assessment of liver function test and its correlation with serum ferritin levels in transfusion-dependent thalassemia patients. Cureus. 2020;12(4): e7574.

16. Sultana I, Sultana N, Rabbany MA, Banu M, Begum S, Alam S et al. Evaluation of Liver Function Tests in β-Thalassemia Major Children. MymensinghMedical Journal: MMJ.2022;31(4):894-899.

17. Akbar M, Nafianti S, Ardiansyah R. The Correlation Between Serum Ferritin and Liver Function in Children with Thalassemia Mayor. The Correlation Between Serum Ferritin and Liver Function in Children with Thalassemia Mayor. 2021;70(1):7-11.

18. Suman RL, Sanadhya A, Meena P, Goyal S. Correlation of liver enzymes with serum ferritin levels in β-thalassemia major. International Journal of Research in Medical Sciences. 2016;4(8):3271-3274.