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RELATIONSHIP OF IRON OVERLOAD WITH CARDIAC COMPLICATIONS IN CHILDREN WITH B THALASSEMIA MAJOR AT A TERTIARY CARE HOSPITAL

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Abstract

Background: *Beta thalassemia major requires lifelong transfusions, leading to iron overload despite chelation therapy. This overload often causes cardiomyopathy, a major cause of mortality. As existing literature shows conflicting results, this study was designed to evaluate the relationship between iron overload and cardiomyopathy.*

Objectives: *1) To determine the frequency of iron overload in thalassemia major children undergoing regular transfusion and iron chelation therapy. 2) To compare the frequency of cardiomyopathy in thalassemia major children undergoing regular transfusion and iron chelation therapy with versus without iron overload.*

Duration: *Four months w.e.f. 18-01-2025 to 17-05-2025.*

Methodology: *Children with beta thalassemia undergoing regular transfusion and chelation at Children's Hospital Lahore were enrolled. Informed consent, demographics, and blood samples were collected. Iron overload and cardiomyopathy were assessed according to operational definitions using T2* MRI. Data were analyzed using SPSS version 25.0.*

Results: *This study included 135 thalassemia major children with a mean age of 10.6±3.6 years. Iron overload was found in 37.8% of patients, with no significant link to age, gender, or chelation type. Cardiomyopathy was significantly higher in children with iron overload (58.8% vs. 32.1%, p=0.002), highlighting strict monitoring needs.*

Conclusion: *The study concludes that iron overload is a critical factor contributing to the development of cardiomyopathy in children with thalassemia major. The findings highlight the importance of effective monitoring and management of iron levels through timely chelation therapy to reduce cardiac complications and improve long-term outcomes in these patients.*

INTRODUCTION

Thalassemia is a genetic disorder characterized by defective or decreased synthesis of α- or β-globin chains, essential components of hemoglobin A. The β-globin genes are located on chromosome 11, while α-globin genes reside on chromosome 16.[1,2] Globally, thalassemia represents a significant health burden,

impacting approximately 72% of 229 countries. An estimated 5.2% of the global population, including 7% of pregnant women and 1% of couples, are at risk of transmitting the disorder.[3] According to WHO, 5% of the population carries the thalassemia gene, with around 17% of newborns affected annually.[4]

Thalassemia major typically presents between six months and two years of age, manifesting in multi-organ damage due to chronic anemia and iron overload.[5] Affected individuals often experience growth delays, facial deformities, endocrine dysfunction, delayed puberty, and cardiopulmonary complications.[6] Management includes regular blood transfusions, iron chelation therapy (ICT), splenectomy, supportive care for complications, and hematopoietic stem cell transplantation the only curative option, though limited by cost and accessibility.[7,8]

Cardiac MRI using T2* sequences remains the gold standard for assessing myocardial iron overload. In Pakistan, where stem cell transplantation remains largely inaccessible, treatment focuses on transfusions and chelation, which have significantly improved life expectancy.[9] However, repeated transfusions lead to secondary iron overload, with the heart being particularly vulnerable. Cardiac complications remain the leading cause of death in β-thalassemia, despite therapeutic advancements.[10]

In a Pakistani study, Hamid et al. [8] reported significant association between iron overload and cardiomyopathy in patients undergoing regular transfusion and chelation therapy (69.57% vs. 30.43%; p-value=0.025) with versus without iron overload. Authors in another Pakistani study by Khalid et al.[11] this association was significant between the groups (76.6% vs. 23.4%; p-value <0.05). Frans et al.[7] in Indonesia reported insignificant relationship between such β thalassemia major patients with versus without iron overload (28.5% vs. 71.5%; p-value=0.264). Similar insignificant relationship was reported by Pepe et al.[2] in Italy between the groups (22.2% vs. 77.8%; p-value>0.05).

Existing data on the relationship between iron overload and cardiac complications in β thalassemia major remain inconclusive and controversial. Therefore, this study was aimed at replicating and validating previous findings to determine whether routine screening for iron overload in regularly transfused β thalassemia major patients is necessary. The results will help guide effective management strategies to prevent cardiac complications and improve patient outcomes in future clinical practice.

METHODOLOGY

This observational analytical study was conducted in the Department of Paediatric Medicine at The Children's Hospital, Lahore, over a duration of four months following the approval of the study synopsis. The sample size consisted of 135 cases, calculated at a 95% confidence level and a 7% margin of error, based on an expected frequency of iron overload of 22.1% in β thalassemia major children undergoing continuous transfusion and chelation therapy.[6] Non-probability consecutive sampling was used for selecting the participants.

Operational definitions used in the study included iron overload, defined by mean serum ferritin levels of ≥2500 ng/mL, and cardiomyopathy, identified by cardiac T2* values of less than 20 milliseconds. Inclusion criteria comprised β thalassemia major patients aged 5 to 16 years, receiving blood transfusions for over one year with at least 10 transfusions since diagnosis, serum ferritin levels above 2500 ng/dL, undergoing regular chelation therapy, and whose parents or guardians provided written informed consent. Patients of both genders were included. Exclusion criteria encompassed children with acute illnesses or inflammatory kidney or liver conditions, known congenital or acquired cardiac diseases, diabetes mellitus, thyroid disorders, ongoing medication such as antibiotics or antiarrhythmics, and other hemoglobinopathies like thalassemia intermedia or sickle cell disease.

Data collection involved enrolling 135 children with beta thalassemia attending the pediatric department, obtaining informed consent, and recording demographics. Blood samples were drawn following standard protocols and sent to the hospital pathology laboratory to assess iron overload according to the operational definitions. Children identified with iron overload were further evaluated for cardiomyopathy using T2* gradient-echo multiecho sequences. All laboratory tests were conducted at a single hospital lab, and cardiac assessments were performed by a single cardiologist to minimize bias. Confounding

variables were controlled through exclusion criteria. Data collection was completed by the resident investigator.

For data analysis, SPSS version 25.0 was used. Numerical variables such as age, disease duration, duration since starting transfusions, and serum ferritin levels were presented as means with standard deviations. Categorical variables, including gender, type of chelation therapy, presence of iron overload, and cardiomyopathy, were expressed as frequencies and percentages. The chi-square test was applied to compare the frequency of cardiomyopathy between patients with and without iron overload, considering a p-value ≤0.05 as statistically significant. Additionally, data were stratified by age, gender, and type of chelation therapy to control for effect modifiers, with chi-square tests applied post-stratification.

RESULTS

The study included a total of 135 participants with a mean age of 10.60±3.58 years. Among them, 64 (47.4%) were aged 5–10 years, while 71 (52.6%) were aged 11–16 years. Regarding gender distribution, 71 (52.6%) were male and 64 (47.4%) were female. In terms of chelation therapy, 65 (48.1%) patients received deferoxamine, whereas 70 (51.9%) were on deferasirox. The mean duration of disease was 9.32±3.54 years, and the mean duration since the start of blood transfusions was 68.44±27.39 months. The mean serum ferritin level was 1912.79±737.45 ng/ml. Assessment of iron load revealed that 51 (37.8%) patients had iron overload, while 84 (62.2%) did not. Data is given in Table 1.0.

Table 2.0 shows that iron overload was present in 39.1% of children aged 5–10 years compared to 36.6% in those aged 11–16 years (p=0.770). Among males, 39.4% had iron overload compared to 35.9% of females (p=0.675). With respect to chelation therapy, 40.0% of children on deferoxamine and 35.7% on deferasirox had iron overload (p=0.608). None of these associations were statistically significant. Table 3.0 shows that cardiomyopathy was significantly more common in children with iron overload compared to those without iron overload (58.8% vs. 32.1%, p=0.002).

Table 4.0 shows that in children aged 5–10 years, cardiomyopathy was observed in 64.0% with iron overload compared to 35.9% without (p=0.028), while in those aged 11–16 years, the frequency was 53.8% versus 28.9% (p=0.037). Among males, 57.1% with overload had cardiomyopathy compared to 32.6% without (p=0.040), whereas in females, it was 60.9% versus 31.7% (p=0.023). Similarly, cardiomyopathy occurred more often in patients receiving deferoxamine (50.0% vs. 23.1%, p=0.025) and in those on deferasirox (68.0% vs. 40.0%, p=0.025).

Table 1.0: Baseline Characteristics of Children include in the Study

Characteristics	Total (135)
Age (years)	10.60±3.58
• 5-10 years	64 (47.4%)
• 11-16 years	71 (52.6%)
Gender	
• Male	71 (52.6%)
• Female	64 (47.4%)
Chelation Therapy	
• Deferoxamine	65 (48.1%)
• Deferasirox	70 (51.9%)
Duration of Disease (years)	9.32±3.54
Duration Since Start of Transfusion (months)	68.44±27.39
Serum Ferritin Level (ng/ml)	1912.79±737.454
Iron Load	

• Iron Overload	51 (37.8%)
• No Iron Overload	84 (62.2%)

Table 2.0: Frequency of Iron Overload Children Stratified for Sub Groups

Characteristics	Iron Overload (n=51)	No Iron Load (n=84)	p-value
Age (years)			
• 5-10 years	25 (39.1%)	39 (60.9%)	0.770
• 11-16 years	26 (36.6%)	45 (63.4%)	
Gender			
• Male	28 (39.4%)	43 (60.6%)	0.675
• Female	23 (35.9%)	41 (64.1%)	
Chelation Therapy			
• Deferoxamine	26 (40.0%)	39 (60.0%)	0.608
• Deferasirox	25 (35.7%)	45 (64.3%)	

Chi Square test, taking p-value≤0.05 as significant

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Table 3.0: Frequency of Cardiomyopathy in Thalassemia Major Children with Versus without Iron Overload

Characteristics	Iron Overload (n=51)	No Iron Load (n=84)	p-value
Cardiomyopathy			
• Yes	30 (58.8%)	27 (32.1%)	0.002
• No	21 (41.2%)	57 (67.9%)	

Chi Square test, taking p-value≤0.05

Table 4.0: Frequency of Cardiomyopathy in Children with Versus without Iron Overload Stratified for Subgroups

Group	Sub Group	Cardiomyopathy		
		Yes	No	p-value
Age (years)	5-10 years	16/25 (64.0%)	14/39 (35.9%)	0.028
	11-16 years	14/26 (53.8%)	13/45 (28.9%)	0.037
Gender	Male	16/28 (57.1%)	14/43 (32.6%)	0.040
	Female	14/23 (60.9%)	13/41 (31.7%)	0.023
Chelation Therapy	Deferoxamine	13/26 (50.0%)	9/39 (23.1%)	0.025
	Deferasirox	17/25 (68.0%)	18/45 (40.0%)	0.025

Chi Square test, taking p-value≤0.05 as significant.

DISCUSSION

Beta thalassemia major is a chronic disorder requiring lifelong blood transfusions. While transfusions improve survival, they result in iron accumulation, necessitating chelation therapy.[12]

Despite chelation, many patients still develop iron overload, which can lead to life-threatening complications, particularly cardiomyopathy, the leading cause of mortality in these children.[13,14] Existing literature shows conflicting evidence regarding the association between iron overload, type of chelation therapy, and risk of cardiomyopathy. Some studies report a strong correlation, while others suggest no significant relationship.[2,7,8,11] To address this controversy and clarify the impact of iron overload on cardiac health, the present study was conducted.

Findings of this study are in line with multiple local and international studies that have explored this relationship. Hamid et al. in Pakistan reported a significant association between iron overload and cardiomyopathy, with 69.57% of patients with iron overload showing cardiac complications, compared to only 30.43% without iron overload ($p = 0.025$).

This study also found a significant association between elevated serum ferritin levels, number of blood transfusions, and electrocardiographic abnormalities, highlighting the predictive value of iron overload for early cardiac dysfunction. Their conclusion emphasized the importance of routine electrocardiographic monitoring in thalassemia patients to detect evolving cardiac complications secondary to iron accumulation.[8]

Similarly, Khalid et al. also from Pakistan found a significant relationship between iron overload and cardiac complications (76.6% in patients with overload vs. 23.4% in those without; $p < 0.05$). Their study emphasized that increasing age, longer transfusion duration, and higher serum ferritin levels were significantly associated with cardiomyopathy, reinforcing the central role of iron overload in the pathogenesis of cardiac dysfunction in thalassemia major.[11]

Contrastingly, Frans et al. in Indonesia reported an insignificant relationship between iron overload and cardiac function ($p = 0.264$). Their study found no significant correlation between serum ferritin levels and systolic or diastolic function of the heart. These findings suggest that serum ferritin alone may not be a reliable indicator of cardiac involvement, and that iron overload may not always result in measurable cardiac dysfunction, at least in early or well-managed cases.[7]

Pepe et al. in Italy also reported an insignificant relationship between serum ferritin levels and cardiac complications (22.2% vs. 77.8%; $p > 0.05$). However, their study highlighted the role of cardiac magnetic resonance imaging in guiding chelation therapy, which led to improved cardiac outcomes. They emphasized that while myocardial iron overload remains a risk factor for heart failure, cardiac magnetic resonance also reveals myocardial fibrosis and structural dysfunctions, providing additional prognostic value beyond iron estimation.[2]

Alama et al. in Saudi Arabia found that although some patients exhibited valvular regurgitations and pulmonary hypertension, left ventricular ejection fraction and serum ferritin alone were insufficient to predict congestive heart failure. They recommended more sensitive methods like cardiac magnetic resonance T2* imaging to identify subclinical myocardial iron deposition.[3]

Supporting this view, Mane et al. in India and Eghbali et al. in Iran found no significant correlation between serum ferritin levels and cardiac T2* values ($p > 0.05$), suggesting that ferritin alone is a poor predictor of myocardial iron overload.[15,16]

Conversely, Heris et al. in Iran reported a modest but significant inverse correlation between serum ferritin and cardiac T2* values ($r = -0.34$; $p = 0.035$), indicating that while some association exists, it is not strong enough for clinical decision-making in isolation.[17]

CONCLUSION

The study concludes that iron overload is a critical factor contributing to the development of cardiomyopathy in children with thalassemia major. The findings highlight the importance of effective monitoring and management of iron levels through timely chelation therapy to reduce cardiac complications and improve long-term outcomes in these patients.

LIMITATIONS & RECOMMENDATIONS

This study's strengths include a well-defined cohort, standardized diagnostic methods, and clinically relevant outcomes. However, being single-center and cross-sectional in nature limits generalizability and causal inference. Reliance on serum ferritin as a marker of iron overload also presents limitations due to its variability. Future research should incorporate larger, multicenter cohorts and advanced imaging tools such as cardiac magnetic resonance imaging T2* to detect subclinical myocardial iron deposition and improve early cardiac risk stratification.

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