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Role of Heart Fatty Acid Binding Protein in Myocardial Dysfunction in Children with β -Thalassemia Major

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ABSTRACT

Background: Beta-thalassemia major (β-TM) is a hereditary hemoglobinopathy condition. For cases with beta thalassemia major, cardiac complications are a significant source of morbidity and death. Cardiac biomarkers showed valuable diagnostic and prognostic role in assessment of cardiac function. **Objective:** This research aimed to assess the role of heart fatty acid binding protein in assessment and confirmation of myocardial dysfunction in kids with β-thalassemia major. **Methods:** This is an observational research that has been performed on 77 kids with β-thalassemia major complicated by asymptomatic LV myocardial dysfunction diagnosed by conventional echo. The kids attended the pediatric Department, Menoufia University Hospital (group 1), and 77 healthy matched kids as a control (group II).

Results: children with beta thalassemia major with myocardial dysfunction had significantly higher heart fatty acid binding protein (HFABP) levels than healthy-matched children. HFABP might be utilized as a good instrument for identification of early myocardial dysfunction in kids with β-TM with an area under the curve of 0.842 (p-value equal to 0.001) at ninety-five percent CI of (0.774-.911). HFABP can be used to diagnose myocardial dysfunction at cut-off value >1.98 pg/mL with 91.34% sensitivity and 63.12 % specificity.

Conclusion: H-FABP has proven to be a valuable biomarker for early recognition of myocardial dysfunction in kids with β-TM, even in the absence of clinical symptoms. Elevated H-FABP levels correlate with subclinical myocardial injury and iron overload, making it a promising tool for early intervention.

Keywords: Myocardial dysfunction, B-thalassemia major, Hemoglobinopathy, Cardiac abnormalities**,** Fatty acid-binding proteins.

INTRODUCTION

One of the genetic hemoglobinopathy illnesses, beta-thalassemia major, is marked by decreased or missing beta-globin chain synthesis, which leads to inefficient erythropoiesis [(1)]. Thus, individuals with β-TM have severe anemia and an overabundance of alpha-globin chains. For survival and the inhibition of inefficient erythropoiesis for the remainder of their lives, affected individuals will require frequent blood transfusions [(2)]. To reverse or avoid problems, lifelong iron chelation therapy is required to treat elevated total body iron [(3)]**.** The mortality and morbidity rates for thalassemia are high. Severe B-TM patients require transfusion for the rest of their lives and initially show signs of increasing anemia in infancy [(4)]. This causes cardiac systolic and diastolic dysfunction by causing iron overload and iron deposition in many parenchymal tissues, involving the heart. Cardiovascular disease is the most common complication among thalassemia patients who need specific medical attention, particularly in children and adolescents [(5)]**.**

The majority of kids with β-TM have cardiac abnormalities, primarily myocardial dysfunction linked to iron overload, which gradually progresses to heart failure and ultimately death. Early treatment is crucial during the reversible stage of cardiomyopathy because chelation therapy may prevent, delay, or reverse cardiac deterioration [(6)]. In patients with ß-thalassemia, cardiac impairment is mostly defined as left ventricular (LV) dysfunction that eventually progresses to heart failure and mortality. Because advanced modalities like 4D and speckle tracking techniques are costly, require specialized knowledge, and are not commonly accessible, echocardiography remains the gold standard for evaluating heart function [(7)].

Studies on the use of cardiac biomarkers have shown that, when paired with traditional echocardiogram, a number of these indicators have useful diagnostic and prognostic roles [(8)]**.** Fatty acid-binding proteins (FABP) are intracellular, tissue-specific molecules that weigh around fifteen kD. These cytoplasmic proteins are crucial for the intracellular use of fatty acids because they bind long-chain fatty acids. Since the architecture and immunology of heart-type fatty acid-binding protein and other forms of FABP differ and there is no cross-reaction, H-FABP is very selective for the recognition of heart damage [(8)]**.** Following myocardial damage, heart-type fatty acid-binding protein is quickly produced into the bloodstream. Children with chronic cardiac disease have elevated serum H-FABP concentrations, which are directly correlated with the advancement of the underlying clinical illness. Myocardial dysfunction can be diagnosed and its severity assessed using serum H-FABP as a biomarker [(9)]**.** To evaluate that aim, this observational controlled study was performed on kids with β-TM complicated by early asymptomatic myocardial dysfunction.

PATIENTS AND METHODS

Study design: This is an observational research that has been performed on 77 kids with β-TM complicated by

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early myocardial dysfunction (dilated left ventricular dimensions with preserved ejection fraction or mildly reduced ejection fraction less than 55% but without clinical symptoms). The children attended the Pediatric Department, Menoufia University Hospital. 77 healthy-matched children as control group during the period from December 2023 to September 2024. All Children were evaluated in the Cardiology Unit of the Pediatric Department in Menoufia University Hospital.

The studied children were divided into two groups:
Group (I) involved 77 kids with asymptomatic LV myocardial dysfunction as the patient group and **Group (II)** included 77 healthy-matched children as a control group. All patients were transfusion-dependent.
Inclusion criteria: Kids with β-TM of both sexes who have myocardial dysfunction diagnosed with conventional echo.
Exclusion criteria: Children suffering from congenital or rheumatic heart disease, any chronic cardiac condition and hematological disorders other than thalassemia.

All study participants underwent comprehensive assessments: Every study subject underwent a thorough history taking, with particular attention paid to the type of chelation therapy, the age at which anemia first appeared, and the frequency and beginning of blood transfusions. An extensive general examination was conducted, emphasizing anthropometric measurements (weight, height, and BMI), vital signs (heart rate, respiration rate, and blood pressure), complete physical investigation including cardiac, abdominal, and chest investigation. Laboratory investigations were done involving CBC, AST, ALT, serum urea, serum creatinine, serum ferritin level, troponin I level and serum H-FABP using ELISA kits.

Transthoracic echocardiographic examination (TTE): Using the Philips HD11 instrument, a transthoracic echocardiographic examination was performed. M-mode and 2-D echo were used in the Echo Doppler examination to determine the left ventricular end systolic and diastolic diameters (LVESD and LVEDD), as well as the fractional shortening (FS%) and ejection fraction (EF%). The E/A ratio, pulmonary end systolic arterial pressure (ESPAP), early peak mitral inflow velocity (E wave), and late atrial contraction wave (A wave) are all measured by a conventional Doppler.

Principle of the assay of human-FABP (h-FABP) and blood sample collection: Prior to tests, blood samples were obtained, centrifuged, aliquoted, labeled, and kept at -80 °C. The quantitative sandwich enzyme immunoassay technique was utilized in this assay. A microplate was pre-coated with an antibody, which is specific to h-FABP. Any heart fatty acid binding protein present is bound by the immobilized antibody following the addition of standards and samples into the wells. A biotin-conjugated antibody that is specific to heart fatty acid binding protein was added to the wells following the elimination of any unbound materials. After washing, the wells were filled with avidin-conjugated horseradish peroxidase (HRP).

Ethical considerations: The authors affirmed that the work presented has been performed according to the World Medical Association's 2013 revision of the Declaration of Helsinki for human experimentation. The Local Ethics Committee of Menoufia University's Faculty of Medicine accepted all study protocols (IRB approval ID, 8/2023 PEDI 14). After outlining the purpose of the research, their parents and guardians gave written informed consents.

Statistical analysis

Statistical analysis has been performed utilizing SPSS version 26 (IBM Inc., Chicago, IL, USA). Quantitative parameters have been represented as mean and standard deviation (SD) and have been examined through unpaired student t-test. Qualitative parameters have been represented as frequency and percentage (%) and have been compared through Chi-square test. Correlations were assessed using spearman correlation. The ROC (receiver operating characteristic) curves to assess the best cutoff values. P-value ≤ 0.05 has been deemed statistically significant.

RESULTS

The study population of 163 kids with B-Thalassemia who have been operated on at the Pediatric Department, Menoufia University Hospital. 9 patients were excluded from the research (3 cases declined consent, 6 didn't fulfil the inclusion criteria), and 154 subjects participated in the study, in which patients have been separated into two groups; group one, involved kids with β-TM with myocardial dysfunction, group two, included control children. Clinical, demographic and laboratory information of the examined groups were presented in table (1) and demonstrated a statistically insignificant variance has been observed among cases and controls concerning age (12.87±2.84 versus11.28±3.1) and sex (males 58.4%, females 42.8% versus males 45.4% versus females 54.5%) respectively. Patients with β-TM have highly statistically significant positive consanguinity in comparison with control group. There was statistically insignificant variance as regards temperature, SBP and DBP between patients and the control groups. However, patients with B-thalassemia had statistically significant lower height, weight and BMI in comparison with the control group, but had significantly higher RR and pulse in comparison with the control group. As regards the laboratory data, there was statistically insignificant variance regarding ALT, AST, urea, creatinine, TLC and platelets between patient and control groups. However, cases with B-thalassemia had significantly lower hemoglobin concentrations and significantly greater serum ferritin, higher serum troponin I and higher serum H-FABP compared to control group.

Table (1): Demographic, clinical and laboratory data of the studied groups

Variables	ß-thalassemia (n=77)	Controls (n=77)	t	*P value*
	Mean ±SD	Mean ±SD		
Age(years) Mean ± SD Median(range)	 12.87±2.84 13(4-18)	 11.28±3.15 11(6-8)	t=1.27	0.092
Sex Male Female	 44(58.4%) 33(42.8%)	 35(45.4%) 42(54.5)	X^2=2.10	0.147
Consanguinity Negative Positive	 36(46.7%) 41(53.2%)	 59(76.6%) 18(23.3%)	X^2=14.53	**<0.001***
Temperature (°c)	37.35±0.22	37.41±0.18	1.736	0.085
RR (breath/min)	23.02±5.02	20.49±3.76	3.539	**0.001***
SBP (mmHg)	116.10±11.25	117.01±11.36	0.499	0.619
DBP (mmHg)	71.81±8.54	72.02±9.12	0.274	0.785
Pulse (bpm)	92.64±9.14	83.10±8.32	6.773	**<0.001***
Weight (kg)	36.96±12.54	41.36±9.43	4.780	**0.013***
Height (cm)	137.74±12.53	143.41±13.41	2.712	**0.007***
BMI (kg/m²)	18.96±3.68	21.34±1.69	5.131	**<0.001***
Hemoglobin (g/dl)	7.82±0.96	12.05±0.59	32.806	**<0.001***
WBC (×10³/mm³)	7.34±1.14	7.87±0.89	0.11	0.93
Platelet (×10³/mm³)	253.6±33.16	236±48.53	2.32	0.061
ALT(U/L)	39.92±9.31	32.20±2.04	1.906	0.058
AST(U/L)	47.77±3.44	43.63±2.75	1.509	0.053
Urea (mg/dl)	26.36±2.34	25.76±3.08	0.22	0.61
Creatinine (mg/dl)	0.54±0.12	0.56±0.1	0.558	0.578
S. ferritin (mg/ml)	2869.67±330.11	68.64±2.47	7.12	**<0.001***
Troponin I (ng/L)	54.16±3.66	1.03±0.13	8.14	**<0.001***
HFABP (mg/dl), Mean ± SD	2.10±0.84	1.21±0.7	U 7.34	**0.001***

Echocardiographic criteria of the studied groups were presented in **table (2**) and showed that LVEDd, LVESd, E, E/A and ESPAP were significantly greater in patients in comparison with control groups, whereas EF, FS and A were significantly lower in thalassemia children.

Table (2): Echocardiographic parameters among the studied groups

	ß-thalassemia (n=77)	Controls (n=77)	*Mann Whitney U test*	
	Mean ±SD	Mean ±SD	U	*P value*
LVE Dd (cm)	4.45±0.73	3.87±0.33	941.0	<0.001*
LVESd (cm)	3.06±0.49	2.44±0.31	785.0	<0.001*
EF (%)	0.59±0.07	0.71±0.07	788.5	<0.001*
FS (%)	0.29±0.03	0.36±0.04	822.0	<0.001*
E (m/s)	1.420±0.031	0.917±0.023	560	0.031*
A (m/s)	0.446±0.124	0.776±0.093	346	0.046*
E/A	2.05±0.43	1.53±0.14	841.5	<0.001*
ESPAP (mmHg)	21.93±4.84	14.18±1.84	419.0	<0.001*

Table (3) showed that HFABP levels were significantly greater among cases with EF < 55% in comparison with cases with EF ≥ 55% (p = 0.041).

Table (3): Relation between HFABP levels and EF%

HFABP levels	**EF%**		**Z**	***P value***
	EF<55% (n=18)	**EF≥55% (n=59)**		
	Mean ±SD	Mean ±SD		
Mean ± SD	1.14±0.81	0.98±0.42	2.11	**0.041***
Range	0.54-3.63	0.59-2.64		
Median	0.78	0.80		

Table (4) and figure (1) showed that utilizing a cut-off value > 1.98 pg/mL with 63.12% specificity and 91.34% sensitivity, receiver operating characteristic (ROC) analysis demonstrated that HFABP concentrations might be a useful instrument for diagnosing asymptomatic myocardial dysfunction in kids with B-TM, with an area under a curve of 0.842 (p-value equal to 0.001) at ninety-five percent CI of (0.774-.911).

Table (4): The cut-off value of H-FABP levels for a prediction of myocardial dysfunction in children with B-thalassemia major

	Area	*Cutoff value* (pg/ml)	*P value*	*Sensitivity %*	*Specificity %*	*95%CI*
HFABP	0.842	>1.98	0.001*	91.34	63.12	0.774-0.911

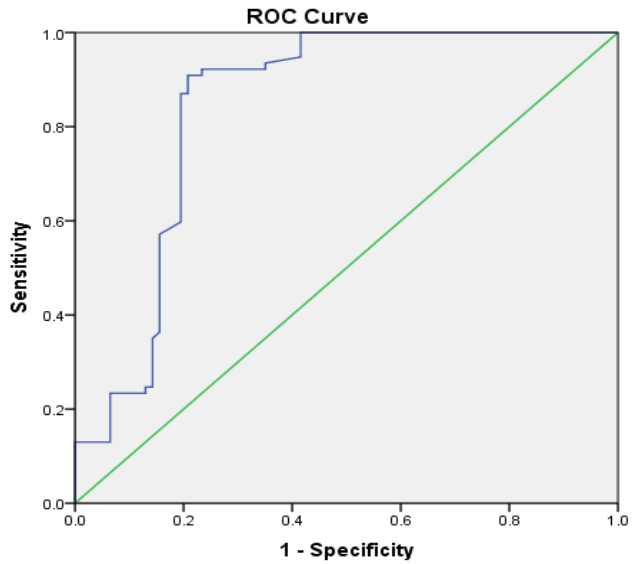

Figure (1): ROC curve of H-FABP levels for a prediction of myocardial dysfunction in children with B-thalassemia major.

DISCUSSION

Beta-thalassemia major (B-TM) is a prevalent genetic disorder that caused by mutations in the β-globin gene, resulting in defective hemoglobin production and severe anemia. This chronic condition often requires frequent blood transfusions, which, over time, can result in iron overload, a major risk factor for cardiac dysfunction [6]. Cardiac complications in thalassemia patients, included heart failure, arrhythmias, and iron-induced cardiomyopathy, which are common causes of morbidity and mortality [9]. Therefore, early recognition of myocardial injury in these cases is crucial for preventing further cardiovascular damage. Heart Fatty Acid Binding Protein (H-FABP) is a sensitive and specific biomarker of myocardial injury, primarily produced from cardiomyocytes into the bloodstream following cell damage. (H-FABP) has demonstrated promise as an early indicator of myocardial dysfunction, often detectable before other traditional biomarkers such as troponin or creatine kinase MB (CK-MB) [8, 10, 11].

To elevate that aim this is an observational study that has been performed on kids with β-TM complicated by myocardial dysfunction who attended Pediatric Department, Menoufia University Hospital. All Kids were evaluated in Cardiology Unit of Pediatric Department in Menoufia University Hospital during the period of the study.

Our study showed that a statistically insignificant variance was observed among children with β-TM and controls in terms of age, sex ($p > 0.05$). However, consanguinity differed significantly ($p < 0.001$), with β-TM patients (53.2%) who showed more positive consanguinity compared to controls (23.3%). A study by **Kadhim *et al.*** [14] indicated that consanguinity significantly increases the risk of homozygosity for β-thalassemia mutations, which in turn contributes to a higher burden of β-TM cases in affected populations. The most common mutations were shared among both consanguineous and non-consanguineous groups, but mutations were more frequently homozygous in consanguineous families.

Our research showed that there were statistically insignificant differences among children with B-thalassemia and controls in terms of temperature, diastolic blood pressure (DBP) and systolic blood pressure (SBP), but significant variances were observed for respiratory rate (RR), pulse, weight, height and body mass index (BMI) (p-value below 0.001). Specifically, BMI, height and weight were lower in β-thalassemia children than control group, while pulse and RR were higher in β-thalassemia children compared to controls. Low BMI, height and weight can be because of chronic anemia, hypoxia, ineffective erythropoiesis, iron overload, frequent blood transfusions, growth hormone deficiency, nutritional deficiencies and anorexia according to **De Sanctis *et al.*** [12]. In this context, **Kadhim *et al.*** [14] additionally, identified a significant variance in body mass index across the groups (p-value below 0.01). This observation aligns with the findings of **Talib *et al.*** [15] who documented that BMI in β-TM cases was significantly reduced in comparison with controls. Also, **Mohammed *et al.*** [8] found that compared to healthy controls, kids with B-TM had significantly reduced height, weight, and body mass index.

Our research also observed that there was statistically insignificant variance as regards ALT, AST, urea, creatinine, TLC and platelets between children with B-thalassemia and control group (p-value above

0.05). However, cases with B-thalassemia had significantly lower hemoglobin in comparison with control group. But had significantly higher serum ferritin, higher serum troponin I compared to control group. **Ayyash *et al.*** [16] align with our results in hemoglobin which was significantly lower in thalassaemic patients and ferritin, which was extremely elevated. Also, it was against our results in liver enzymes & kidney markers as they were significantly greater in cases in comparison with controls. Most patients in **Basri's** [17] research had ferritin concentrations ≥ 1,000 ng/ml (89.1%), which is consistent with **Mahmoud *et al.*** [18] findings of a significantly elevated mean ferritin level of 2820.55 ± 742.81 ng/ml in β-thalassemia patients compared to controls. Similarly, **Talib *et al.*** [15] confirmed a significant elevation in serum ferritin concentrations in β-thalassemia major cases**.** Furthermore, in a related study, **Altın *et al.*** [19] reported a median ferritin level of 1,581 ng/mL (range: 220–6,214 ng/mL) among β1thalassemia patients.

Our study also demonstrated that there was statistically significant variance regarding HFABP in kids with B-Thalassemia and the control group (P-value below 0.001). H-FABP is greater in cases with B-thalassemia with myocardial dysfunction**. Kadhim *et al.*** [14] reported that serum H1FABP concentrations in Beta-thalassemia major cases were significantly greater compared to those in the control group. These results align with **Mohammed *et al.*** [8] who observed that thalassemia patients without previous cardiac dysfunction manifestations had greater serum Heart Fatty Acid Binding Protein levels compared to healthy kids.

H-FABP showed superiority over traditional biomarkers for assessing recurrent or persistent myocardial damage in various classes of heart diseases. Interestingly, an elevated H-FABP level can recognize cases at possibility for mortality and major cardiac events, even when levels of troponins and CK-MB remain within normal ranges according to **O'Donoghue *et al.*** [20]**.** Furthermore, **Sun *et al.*** [21] highlighted that H-FABP is sensitive to ongoing myocardial damage and can recognize cases at great possibility of heart failure. Numerous factors might contribute to the elevation of H-FABP concentrations in Beta-thalassemia.

Firstly, Beta-thalassemia results in abnormal or reduced hemoglobin production and iron overload, leading to hemolysis and chronic anemia as said by **Akiki *et al.*** [6]**.** This condition increases cardiac output and impairs blood flow and oxygen delivery to the heart, which can result in cardiac injury and elevated H-FABP levels showed by **Li *et al.*** [22]**.** Moreover, frequent blood transfusions in thalassemia patients exacerbate iron overload, causing oxidative stress, inflammation, and cardiac cell damage, thereby releasing H-FABP into the bloodstream as mentioned by **Wood *et al.*** [23]**.**

Our study also demonstrated that there was statistically significant variance regarding echocardiographic parameters. The LVED, LVESd, E, E/e`, E/A and ESPAP were significantly greater in children with B-Thalassemia in comparison with control children, while EF, FS, A, e', a' and S 'were significantly reduced in thalassaemic cases compared to controls. As regards LVEDd and LVESd, **Altaher *et al.*** [24] observed that LVEDd showed a significant increase in thalassemia patients aged 6–12 years compared to controls (p = 0.03). Nevertheless, this variance was insignificant in older patients (p-value equal to 0.1), likely due to compensatory cardiac mechanisms to manage volume overload. Changes in heart rate, LV mass and contractility—driven by increased sympathetic activity—may contribute to this normalization with age. Furthermore, **Mohammed *et al.*** [8] observed that β-thalassemia major patients exhibited significantly greater ventricular dimensions. Moreover, **Deraz *et al.*** [1] demonstrated LV end-systolic and end-diastolic dilatation in β1thalassemia major patients. **Ibrahim *et al.*** [25] concluded that increased LV dimensions were among the earliest echocardiographic signs of dilated cardiomyopathy in β-TM cases reinforcing the importance of early and ongoing cardiac monitoring in this population.

Regarding systolic function, **Altaher *et al.*** [24] found that EF and FS did not differ significantly in younger patients (p = 0.48 & 0.27 respectively). However, in older age groups, EF and FS were significantly reduced (p = 0.004, 0.004 respectively), likely due to chronic anemia and elevated iron levels that impair cardiac contractility. These results align with other investigations through **Morris *et al.*** [26]**. Arshad *et al.*** [27] reported reductions in EF and FS without statistical significance.

As regard diastolic myocardial dysfunction that has also been documented in β-thalassemia patients, **Yavuz *et al.*** [28] showed that restrictive diastolic dysfunction was characterized by high E values and E/A ratios, linked to iron accumulation in the heart. **Altın *et al.*** [19] corroborated these findings, reporting increased E/A and E/e ratios that progressed with age. **Ibrahim *et al.*** [25] showed that S′ and a 'were significantly reduced in B-thalassemia cases compared to healthy group.

As regards estimated systolic pulmonary arterial pressure, **Mohammed *et al.*** [8] observed that β-TM patients exhibited significantly greater ESPAP in comparison with healthy controls. Also **Morris *et al.*** [26]**, Agarwal *et al.*** [29] & **Chuncharunee *et al.*** [30] observed that children with B-thalassemia had significantly greater ESPAP. All of the echocardiographic observations listed above are consistent with previous publications that found myocardial dysfunction, including systolic and diastolic dysfunction linked to transfusion. **Taksande *et al.*** [31] utilizing a cut-off value >1.98 pg/ml with 63.12% specificity and 91.34% sensitivity, ROC analysis demonstrated that HFABP concentrations might be a useful instrument for diagnosing myocardial dysfunction in kids with β-TM with an area under a

curve of 0.842 (p-value equal to 0.001) at ninety-five percent CI of (0.774-.911).

CONCLUSION

Heart Fatty Acid Binding Protein proved to be a valuable biomarker for early recognition of myocardial dysfunction in kids with β-TM even in the absence of clinical symptoms. Elevated H-FABP levels correlate with subclinical myocardial injury and iron overload, making it a promising tool for early intervention.

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