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ASSESSMENT OF SERUM LEVEL OF BETA- 2 MICROGLOBULIN IN ADULT PATIENTS WITH BETA THALASSEMIA MAJOR

Zainab Mohammed Hussein Abd Al-Ameer*[1] and Hind Shaker[2]

[1]Baghdad- Al-Karkh Health Directorate, Baghdad, Iraq.
[2]Al-Nahrain College of Medicine, Al-Nahrain University, Baghdad, Iraq.

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***Corresponding Author: Zainab Mohammed Hussein Abd Al-Ameer**
Baghdad- Al-Karkh Health Directorate, Baghdad, Iraq.

ABSTRACT

Background: Beta Thalassemia is an autosomal recessive hereditary hemoglobinopathy characterized by reduced or absent beta-globin chain production. Management primarily involves regular blood transfusions, which can lead to iron overload affecting organs such as the heart, liver, endocrine glands, and kidneys. Renal dysfunction in Beta Thalassemia may result from iron overload, oxidative stress, thrombosis, or as a side effect of iron chelation therapy. β-2 microglobulin, a low-molecular-weight protein filtered by glomeruli and reabsorbed in proximal tubules, serves as a sensitive marker for renal tubular injury and oxidative stress. Aims of Study: To measure serum β-2 microglobulin levels in adults with Beta Thalassemia major and assess its utility as a sensitive renal function marker. To evaluate correlations between β-2 microglobulin, hematological parameters, transfusion frequency, and serum ferritin levels. **Patients and Methods:** A case-control study was conducted from January to October 2024, including 60 adult Beta Thalassemia major patients and 20 healthy controls. Blood samples were collected before transfusion for CBC, urea, creatinine, ferritin, and β-2 microglobulin, the latter measured via ELISA. **Results:** Mean age was 22.4±5.3 years; 60% were male. Patients had significantly lower hemoglobin, MCV, and MCH, with higher RDW, platelet count, ferritin, and β-2 microglobulin levels ($p<0.001$). β-2 microglobulin negatively correlated with GFR and positively with serum ferritin, urea, creatinine, and transfusion frequency. **Conclusions:** Iron overload, chronic anemia, and chelation toxicity contribute to renal impairment in Beta Thalassemia major. Elevated β-2 microglobulin levels indicate renal dysfunction and correlate with transfusion burden and iron overload, highlighting its role as a sensitive renal marker.

KEYWORDS: serum level, Beta- 2, Microglobulin, adult, Beta thalassemia major.

INTRODUCTION

Thalassemia represents a group of inherited hematologic disorders characterized by a reduced rate of synthesis of one or more globin chains, leading to imbalanced globin chain production. This imbalance results in defective hemoglobin formation and damage to red blood cells or their precursors due to the accumulation of unpaired globin chains.[1] Among these, β-thalassemia is further classified into β^0-thalassemia, where there is a complete absence of β-globin chain production, and β^+-thalassemia, which is marked by partial reduction in β-chain synthesis.[1] The clinical manifestations of β-thalassemia vary depending on the genetic mutation's severity. Patients with mild mutations may remain asymptomatic, while those with severe mutations often suffer from anemia, hepatosplenomegaly, increased susceptibility to infections, gallstones, and skeletal deformities, particularly of the facial bones.[2] Beta Thalassemia Major (BTM) is the most severe form and typically necessitates lifelong regular blood transfusions, starting before the age of two. Without appropriate treatment, affected individuals often succumb in early life.[3] Conversely, individuals with β-thalassemia intermedia may initially require minimal transfusion support but may develop increasing transfusion needs as they age.[3] Chronic blood transfusion therapy, though life-saving, contributes to iron overload, a major complication of the disease. Each unit of transfused blood introduces approximately 200–250 mg of iron, far exceeding the body's natural iron absorption limit of 1 mg per day.[4] Excess iron accumulates in vital organs such as the heart, liver, endocrine glands, and kidneys, leading to progressive organ damage. Thus, the administration of iron chelators becomes essential to enhance patient survival and quality of life.[5, 6] Renal dysfunction in patients with thalassemia can arise due to

multiple mechanisms including iron overload in renal tissues, oxidative stress from free radical generation, thrombosis, and as an adverse effect of iron chelation therapy such as desferrioxamine (DFO).[7] Serum ferritin remains a widely used marker to evaluate body iron burden due to its accessibility, affordability, and feasibility for repeated testing.[8] In recent years, β-2 microglobulin (β2M), a low-molecular-weight protein (11.8 kDa), has emerged as a potential biomarker for early renal impairment. As a component of the light chain of HLA class I molecules, β2M is present on all nucleated cells, freely filtered by the glomeruli, and reabsorbed by the proximal tubules.[9] Its elevated serum levels indicate proximal tubular dysfunction and are also associated with inflammatory, immunologic, and neoplastic disorders.[10] The aim of study is to measure the blood level of Beta 2-Microglobulin in adults with Beta thalassaemia major to determine its renal function sensitivity. Beta2-microglobulin, haematological parameters, transfusion frequency, and ferritin levels should be correlated.

METHOD

This case-control study was conducted over a ten-month period, from January 4 to October 31, 2024, at the Thalassemia Center in Al-Zahraa Teaching Hospital, Najaf. The study included 80 participants divided into two groups: Group I consisted of 60 adults, non-splenectomized patients diagnosed with β-thalassemia major, while Group II included 20 age- and sex-matched apparently healthy individuals as controls. Diagnosis of thalassemia was confirmed based on clinical findings and laboratory investigations including complete blood count (CBC), peripheral blood smear, and high-performance liquid chromatography (HPLC), with all diagnostic data obtained from medical records. Informed verbal consent was obtained, and the study received ethical approval from both the Iraqi Board for Medical Specializations and the Najaf Health Directorate. Five milliliters of peripheral venous blood were collected under aseptic conditions prior to blood transfusion. Two milliliters were placed in EDTA tubes for CBC and blood urea analysis, while the remaining blood was collected into gel tubes, allowed to coagulate in a 37°C water bath, and centrifuged at 2000 g for 5 minutes to obtain serum. Serum samples were used for creatinine, ferritin, and β-2 microglobulin analysis. Samples for β-2 microglobulin were stored at –40°C until assessed by sandwich ELISA using a human β-2 microglobulin ELISA kit. CBC was analyzed using the Sysmex XN 1000 analyzer (Japan). Renal function tests including serum creatinine and blood urea were measured using the SIEMENS Atellica CH 930 analyzer (Germany). Glomerular filtration rate (GFR) was calculated using the 2021 CKD-EPI creatinine formula; renal dysfunction was defined as GFR <90 ml/min/1.73 m². β-2 microglobulin was quantified via ELISA, based on absorbance at 450 nm following color development with TMB substrate. Data were analyzed using SPSS version 26. Quantitative variables were assessed for normality using the Shapiro-Wilk test. Appropriate statistical tests, including Chi-square, Mann-Whitney U test, and Pearson correlation, were applied, with significance set at $p \leq 0.05$.

RESULTS

Patients' age ranged from 17 to 39 years. No statistically significant difference of age was observed between patients (22.4±5.3) and controls (24.5±5.9), p-value = 0.06.

Males comprised 60% (36/60) of the total study population while females formed the remaining 40% (24/60) of them. No statistically significant difference in sex distribution was observed between patients and controls, p-value = 0.4. **(Table 1)**

Table (1): Age and sex distribution of the studied groups.

		Group		Total	P value
		Patients (n=60)	Controls (n=20)		
Age (year)#		22.4±5.3	24.5±5.9	23.5±3.6	0.06
Sex ##	Male	36(60%)	10(50%0	46(57.5%)	0.4
	Female	24(40%)	10(50%)	34(42.5%)	

CBC parameters (RBC, Hb, MCV, MCH, RDW, WBC and PLT) of patients and control were compared, there was significant differences between the two groups regarding Hb with p-value < 0.001, considering RBC indices there were significant differences in MCV, MCH and RDW with p-value <0.001 while there were no significant differences in WBC with p-value = 0.07 between patients and control. Serum ferritin level was significantly higher in TM group compared to controls group with p-value= 0.0001 **(Table 2)**

Table (2): Comparison of hematological parameters between thalassemic patients and controls. Comparison of serum ferritin between thalassemia patients and controls.

	Patients (n=60) Mean± SD	Controls (n=20) Mean ±SD	P value
RBC	2.8±0.5	4.4±0.7	0.0001*
Hb (g/dl)	7.4±1.2	12.8±1.5	0.0001*
MCV (fl)	74.2±5.6	82±2.1	0.0001*
MCH (pg)	25.7±2.3	26.9±1.3	0.006*

RDW	**17.4±4.04**	**13.7±0.9**	**0.0001***
WBC	**6.4±3.2**	**5.9±2.1**	**0.07**
PLT	**320.95±207.5**	**238.15±71.5**	**0.01***
	Patients (n=60) Mean±SD	**Controls (n=20) Mean±SD**	**P Value**
S. Ferritin(ng/dl)	**2214±1951.1**	**119.8±37.7**	**0.0001***

Biochemical parameters of patients and control were compared, there was significant differences between the two groups with p-value < 0.01, as in table 3.

Table (3): Comparison of biochemical parameters between thalassemic patients and controls.

	Patients (n=60) Mean±SD	Controls (n=20) Mean±SD	P value
B.Urea (mg/dl)	**33.9±5.9**	**23.9±5.5**	**0.0001***
S.CR (mg/dl)	**0.9±0.2**	**0.5±0.2**	**0.0001***
GFR(ml/min/1.73m²)	**111.9±22.5**	**137.7±12.7**	**0.0001***
S.ß2M (ng/dl)	**3.7±1.7**	**1.8±0.9**	**0.0001***

There was a strong negative correlation between serum **β-2 M** level and Hb and GFR with p value <0.01 while it is positively correlated with S.Ferritin, B.Ura, S.creatinine and blood transfusion per year with p-value <0.001. **(Table 4)**.

Table (4): Correlations between S.ß-2M and renal function parameters, ferritin, Hb and frequency of blood transfusion/year.

Variables	S. Beta 2-Microglobulin	
	r	p
Blood transfusion/ year	**0.929****	**0.0001***
S. Ferritin (ng/dl)	**0.893****	**0.0001***
GFR (ml/min/1.73m²)	**-0.989****	**0.0001***
B.Urea(mg/dl)	**0.457****	**0.0001***
S.CR (mg/dl)	**0.857****	**0.0001***
Hb (g/dl)	**-0.393****	**0.002***

There was a significant positive correlation between urea, Ferritin and frequency of blood transfision /year with p 0.006; p 0.001, respectively. There was also another positive correlation between serum creatinine, Ferritin and frequency of blood transfision /year with p<0.001, while it had a negative correlation with Hb at p value 0.05. There was a significant positive between GFR and Hb with p value 0.004, while it had a negative correlation with Ferritin and frequency of blood transfusion /year with p value <0.001. **(Table 5)**

Table (5): correlation of hematological parameters with parameters indicating renal function among thalassemia patients.

	Hb r	P V.	Ferritin r	P V.	Freq. of blood transfusion/ year	P V.
B. Urea (mg/dl)	**0.2**	**0.2**	**0.350**	**0.006****	**0.422**	**0.001****
S. Creatinine (mg/dl)	**-0.3**	**0.05***	**0.771**	**0.0001****	**0.841**	**0.0001****
GFR (ml/min/1.73m²)	**0.363**	**0.004****	**-0.913**	**0.0001****	**-0.957**	**0.0001****

. ***Correlation is significant at the 0.01 level (2-tailed).*

. ***Correlation is significant at the 0.05 level (2-tailed).

There was a strong positive correlation between freq. of blood transfusion /year and serum ferritin in TM patients with p value <0.001. ROC Curve analysis of Beta 2-Microglobulin revealed at cutoff 4.1 ng/dl, Beta 2-M gave 92% sensitivity, 95% specificity, and AUC = 0.9 for renal impairment in BTM pts. As in table 6.

Table (6): Correlation between frequency of blood transfusion /year with serum ferritin. Diagnostic accuracy of β 2-Microglobulin as a diagnostic tool for renal impairment in thalassemia pts.

		S. ferritin Median(IQR)	P value
Frequency of transfusion/ year	**<12**	**687(297)**	**0.0001***
	> 12	**3852.5(3619)**	

Characteristics	Cutoff point	Sensitivity	Specificity	AUC
Beta 2-Microglobulin	**4.1 ng/dl**	**92%**	**95%**	**0.9**

DISCUSSION

Thalassemia is a genetic disorder marked by reduced synthesis of one or more globin chains, resulting in defective hemoglobin production and chronic anemia.[1] In β-thalassemia major (β-TM), continuous blood transfusions and iron chelation therapy are required to manage anemia and prevent iron overload complications. Among the critical consequences of iron overload is renal dysfunction, which is frequently under-recognized but increasingly acknowledged in thalassemia patients. In this study, we assessed renal function in β-TM patients and explored the significance of β-2 microglobulin (β2M) as an early biomarker of renal impairment. Renal dysfunction in β-TM is multifactorial, involving iron deposition in the renal parenchyma, chronic hypoxia due to anemia, and nephrotoxic effects of chelating agents such as desferrioxamine (DFO).[13-11] β2M is a low-molecular-weight protein filtered by glomeruli and reabsorbed by proximal tubules, and its elevation in serum is indicative of renal tubular dysfunction.[12,13] In this study, serum β2M levels were significantly higher in β-TM patients compared to healthy controls (p=0.0001), corroborating findings by Behairy et al.[14], Zafari et al.[15], and Vaskaridou et al.[16], who also reported significantly elevated β2M in thalassemia patients, suggesting subclinical renal impairment likely due to renal hemosiderosis. In agreement with previous studies[17,18], our patients demonstrated significantly lower hemoglobin, MCV, MCH, and RBC counts, consistent with ineffective erythropoiesis. A compensatory increase in platelet count was observed, likely secondary to anemia-induced marrow stimulation.[19] Serum ferritin was also markedly elevated in thalassemia patients, reflecting iron overload due to repeated transfusions.[20] This increase in ferritin has been associated with impaired renal function, as iron deposition promotes oxidative stress and tubular damage.[21] Renal function markers including blood urea and serum creatinine were significantly elevated in β-TM patients, with reduced GFR levels, consistent with studies by Ali and Mahmoud et al.[21]and Behairy et al.[14] Although other studies such as Zafari et al.[15] reported no significant difference in creatinine levels, this inconsistency may be due to the variability in muscle mass, protein intake, and liver function among patients, which influence creatinine levels.[22] Our findings reinforce the need for more sensitive and specific renal markers like β2M. Strong positive correlations were observed between β2M and frequency of blood transfusions, serum ferritin, urea, and creatinine, and a strong negative correlation with GFR and hemoglobin. These associations support findings from Behairy et al.[14], Donido et al.[23], and Vaskaridou et al.[16], who also reported inverse relationships between β2M and renal function parameters. Our findings affirm that lower hemoglobin and higher iron overload are associated with greater renal dysfunction. Furthermore, GFR showed a significant positive correlation with hemoglobin and an inverse correlation with ferritin, aligning with studies by Zhu et al.[24], Khan et al.[25], and Elbedewy et al.[26], all of whom reported impaired renal function in patients with high ferritin and low hemoglobin levels. These results highlight the deleterious impact of iron overload and anemia on kidney health. Lastly, the best cutoff value for β2M in our study was 4.1 ng/dL, with 92% sensitivity and 95% specificity (AUC = 0.9), closely aligning with Behairy et al.[14], who reported 85.7% sensitivity and 100% specificity. This supports the utility of β2M as a reliable and early marker of renal impairment in β-TM patients.[27]

CONCLUSION

Patients with β thalassemia major may experience renal impairment due to iron overload, chronic anemia, and chelation treatment toxicity, as shown by GFR, hemoglobin, blood transfusion frequency, and serum ferritin Serum β-2 M levels are elevated in β-thalassemia Major patients relative to healthy controls, and are linked to GFR, s. creatinine, and blood urea, indicating renal function impairment. Elevated s. ferritin and frequent blood transfusions can harm renal function, resulting in low GFR and elevated β-2 M.

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