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Research Article

Human β2-Microglobulin: Can use as Early Diagnostic Tool for Pediatric Patients with β Thalassemia Major and Intermedia?

Soad Abd ElMoaty Salah[1]*, Ibrahim Mohamed Eladel Abouelkhir[1], Ibrahim Ezzelregal Shamah[1]

[1]Department of Pediatric, Shebin El-Kom Teaching Hospital, Shebin El-Kom 32511, Menoufia, Egypt.

***Corresponding Author:** Soad Abd ElMoaty Salah, Department of Pediatric, Shebin El-Kom Teaching Hospital, Shebin El-Kom 32511, Menoufia, Egypt.

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Abstract

Background: β-thalassemia syndromes are inherited disorders caused by defective β-globin chain synthesis, leading to ineffective erythropoiesis, severe microcytic hypochromic anemia, and progressive iron overload. β-thalassemia major results from mutations in both β-globin genes, whereas thalassemia intermedia presents with intermediate clinical severity and relatively preserved hemoglobin levels without regular transfusions. Although thalassemia primarily affects cardiopulmonary and reticuloendothelial systems, renal involvement is often underrecognized. Therefore, accurate estimation of glomerular filtration rate (GFR) is essential in pediatric β-thalassemia, as traditional markers such as serum creatinine and creatinine clearance may yield misleading results.

Methods: Fifty children of Beta thalassemia (major and intermedia) disease participated in the present study. Their age ranged from 3 to 18 years. Patients were selected from the outpatients attending the pediatric hematology clinic and the inpatients of shebein elk om teaching Hospital.

Results: There was significant positive correlation between B2M and age, frequency of transfusion, serum ferritin ($P<0.05$), highly significant positive correlation between B2M and Duration of chelation, S urea, serum creatinine, Na, K, Ca and Ph ($P<0.001$), significant negative correlation between B2M and Hb, age at start of transfusion (<0.05), and highly significant negative correlation between ween B2M and C Cr 24-hour urine ($P<0.001$).

Conclusion: All thalassemia patients will need more proper control of iron overload. Our data indicates that renal impairment is not rare in β thalassemia. Urine β2 microglobulin is a positive sensitive marker of renal tubular dysfunction especially in thalassemic pediatrics patients. Further studies are needed to investigate the role of new chelators in tubular function parameters, such as urine electrolytes and β2M excretion.

Keywords: β2-microglobulin, Diagnostic tool, Pediatric patients, Thalassemia, Deferoxamines.

Key Message

- Renal involvement is common in pediatric β-thalassemia and may be underestimated; β2-microglobulin shows strong correlations with iron overload, transfusion burden, chelation duration, and conventional renal function parameters.
- Urinary β2-microglobulin is a sensitive marker of early renal tubular dysfunction in children with β-thalassemia, demonstrating significant negative correlation with hemoglobin levels and creatinine clearance.
- Optimal iron overload control is essential in β-thalassemia patients, and further research is needed to assess the impact of newer iron chelators on renal tubular function and β2-microglobulin excretion.

Introduction

Thalassemia is a hereditary anemia resulting from genetic disorders of hemoglobin synthesis. It is not a single disease but a group of disorders, each resulting from an inherited abnormality of globin production. The conditions form part of the spectrum of diseases known collectively as the hemoglobinopathies, which can be classified broadly into two types [1].

There are two types of thalassemia, alpha thalassemia and beta thalassemia. Beta thalassemia occurs in people of Mediterranean origin and, to a lesser extent, Chinese, other Asians, and African Americans. It is caused by a mutation in the beta globin chain. Affected children are normal at birth but develop anemia during the first year of life. Beta Thalassemia major (B-TM) is a genetic blood disease caused by mutations on chromosome 11 that cause a decrease in the production of (beta) globin chains. The ensuing abnormal globin chain ratio results in ineffective erythropoiesis, hemolysis and severe anemia. To survive, patients with B-TM require regular blood transfusions, which lead to a progressive tissue accumulation of iron [2].

So, it is very important to use regular chelation therapy for management of iron overload in thalassemia: deferoxamines (DFO) used subcutaneous or intravenous but have side effect irritation at infusion sites, ocular and auditory disturbance growth retardation and skeletal changes. Deferiprone taken oral used when DFO therapy is contraindicated or inadequate side effect agranulocytosis and neutropenia increased liver enzyme. Deferasirox (exjade) taken oral, side effect gastrointestinal disturbances, rash increase in serum creatinine level potentially fetal renal and hepatic impairment of failure gastrointestinal hemorrhage. Human β2-microglobulin (β2-M) is a low-molecular-weight protein that forms part of the major histocompatibility complex class I and is present on the surface of nearly all nucleated cells. In healthy individuals, serum β2-M levels are generally low but increase in conditions associated with inflammation, immune activation, or tissue damage [3].

In pediatric patients with β-thalassemia major, chronic hemolysis, iron overload from regular blood transfusions, and oxidative stress contribute to subclinical organ dysfunction, including renal injury. Multiple studies have shown that children with β-thalassemia major have significantly higher serum β2-microglobulin levels compared with healthy controls, indicating its potential utility as an early biomarker of glomerular and tubular dysfunction, often before changes in conventional markers like creatinine are observed. Serum β2-microglobulin correlates positively with clinical parameters such as serum ferritin, duration of chelation therapy, and frequency of transfusions, and negatively with estimated glomerular filtration rate (eGFR) and hemoglobin, suggesting its role in detecting early kidney dysfunction in this population [4].

Beyond renal assessment, β2-microglobulin levels can reflect broader pathophysiological changes in children with chronic diseases. Although the most direct evidence in β-thalassemia focuses on renal implications, research in related pediatric disorders illustrates how elevated β2-microglobulin may serve as a sensitive marker of systemic involvement, including immune and inflammatory processes. In conditions like congenital heart disease with heart failure, pediatric patients also demonstrated significantly increased β2-microglobulin levels that correlated with disease severity, highlighting its potential as a general biomarker of chronic disease burden in children [5]. This supports the concept that in β-thalassemia, elevated β2-microglobulin may not only indicate early renal dysfunction but could also reflect ongoing inflammation, immune activation, and cumulative organ stress stemming from iron overload and chronic anemia. The purpose of this research was to the use of Human β2-microglobulin for pediatric patients with β thalassemia major and intermedia.

Patient and Methods

Study Design and Patient Setting

In this study we included subjects that had a diagnosis of B thalassemia major, or intermedia documented by hemoglobin electrophoresis, they were regularly transfused with packed RBCs, and Subjects were receiving ongoing chelation therapy with deferoxamines or deferiprone mostly in an irregular manner. However, the following criteria were excluded from this study, previous renal pathology and previous treatment for thyroid dysfunction.

Ethical Consideration Statment

The study complied with the World Medical Association's Declaration of Helsinki, according to the authors. The local committee of the shebein elk om teaching Hospital at Menoufia University approved all study methods. The advantages, possible hazards, and every stage of the procedure were explained to all participants. Before taking part in the research, each participant signed an informed consent form.

Patients' Selection Criteria

A total of fifty children diagnosed with β-thalassemia (major and intermedia) were enrolled in the present study, with ages ranging from 3 to 18 years. Patients were recruited from both the outpatient pediatric hematology clinic and inpatient wards of Shebein El-Kom Teaching Hospital. The study population was classified into two main groups: Group I (thalassemia patients), which included Group Ia comprising 35 children with thalassemia major (12 males and 23 females) aged 3–20 years with a mean age of 11.24 ± 4.87 years, and Group Ib comprising 15 children with thalassemia intermedia (7 males and 8 females) aged 4.5–20 years with a mean age

of 12.23 ± 5.17 years. Group II (control group) consisted of 20 apparently healthy children matched for age (3–19 years, mean 11.0 ± 4.67 years), sex (10 males and 10 females), and socioeconomic status.

All Patients were Subjected to

Routine laboratory investigations were performed for all participants and included a complete blood count (CBC) using the ADVIA® 2120 automated hematology analyzer (Siemens, Germany) to assess hemoglobin concentration and red blood cell indices, including MCV, MCH, MCHC, and RDW. Renal function was evaluated by measuring serum creatinine using the modified rate Jaffe method. Special laboratory investigations included assessment of renal tubular function through measurement of urinary β2-microglobulin (μg/L), estimation of creatinine clearance based on 24-hour urine collection, and quantitative determination of β2-microglobulin levels in urine. β2-microglobulin was measured using an in vitro diagnostic reagent based on particle-enhanced immunonephelometry on BN* Systems (AXSYM, Ireland), applicable for quantitative determination in human serum, heparinized and EDTA plasma, as well as urine.

Principle of the Urinary β2-microglobulin

Urinary β2-microglobulin was measured using a particle-enhanced immunonephelometric method, in which polystyrene particles coated with specific antibodies against human β2-microglobulin aggregate upon interaction with the antigen present in the sample, resulting in light scattering proportional to the β2-microglobulin concentration and quantified by comparison with a standard of known concentration. Serum creatinine was determined using the modified Jaffe reaction, where creatinine reacts with picric acid in an alkaline medium to form a yellow-red complex, with absorbance measured at 492 nm and directly proportional to creatinine concentration. Creatinine clearance was calculated according to the Schwartz et al. (1987) formula using 24-hour urine collection, based on urinary creatinine concentration, plasma creatinine concentration, and total urine volume, with normalization to a body surface area of 1.73 m² to correct for variations in muscle mass and creatinine excretion.

Statistical Analysis Methods

The collected data were tabulated and statistically analyzed using an IBM personal computer and the Statistical Package for Social Sciences (SPSS), version 11. Descriptive statistics were expressed as mean, standard deviation (SD), and percentages. Analytical statistics included the chi-square (χ^2) test to assess associations between qualitative variables; Student's t-test for comparison between two groups with normally distributed quantitative variables; and the Mann–Whitney U test for comparison between two groups with non-normally distributed quantitative variables. Comparisons among three or more groups were performed using one-way analysis of variance (ANOVA) for normally distributed data and the Kruskal–Wallis test for non-parametric data. Pearson's correlation coefficient (r) was used to evaluate associations between quantitative variables. Receiver operating characteristic (ROC) curves were constructed to assess diagnostic performance, and the cutoff value with the highest diagnostic accuracy was selected. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were calculated using standard formulas. A P-value of less than 0.05 was considered statistically significant.

Results

According to a workflow diagram that describes the cohort of 126 children with HCV infections who enrolled at Menoufia University's National Liver Institute, 6 individuals weren't included in the study (2 denied consent and 4 did not match the inclusion criteria). This led to the inclusion of 120 patients in the research. A total of 98 patients were assigned to the ≤F2 group, while 22 more patients were assigned to the >F2 group (Figure 2). The descriptive information about the study participants is shown in Table 1. Of the individuals we evaluated, 82% had ≤F2 at presentation, while 18% had >F2 (Figure 1).

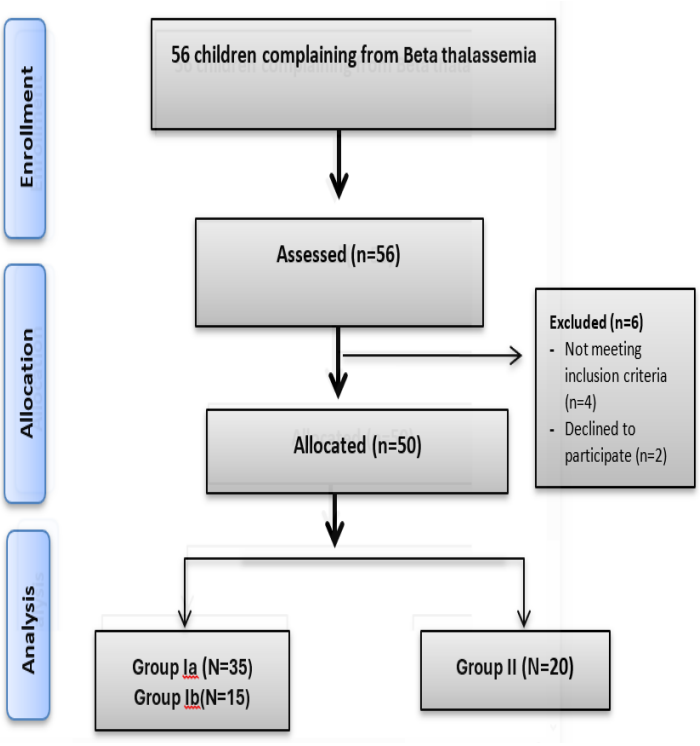

Figure 1. Flowchart of the patients studied.

In the current study there is non-significant difference between the studied groups regarding to age, sex (P>0.05),

(Table 1). The current study found highly positive significant decrease in the Hb level and increase regarding serum ferritin among thalassemia group and control(P<0.001). While it shows a non-significant difference between both types of thalassemia regarding to Hb and ferritin level (P>0.05), (Table 2).

Demographic data	Thalassemia major (n=35)		Thalassemia intermediate (n=15)		Control (n=20)		X2	P value
	No	%	No	%	No	%		
Sex								
Male	12	34.3	7	46.7	10	50	1.51	>0.05
Female	23	65.7	8	53.3	10	50		
Age in years								
Mean ±SD	11.24 ± 4.87		12.23 ± 5.17		11.0 ± 4.67		F=0.42*	>0.05
Range	3-12		4.5-20		3-19			

Chi-square test (X2), standard error (SD), ANOVA F-test (F)

Table 1. Comparison between studied groups regarding demographic data.

Parameter	Thalassemia major (n=35)	Thalassemia intermediate (n=15)	Control (n=20)	F	P value
Hb (g/dl)					P1>0.05
Mean ±SD	6.03 ± 0.79	6.47 ± 0.89	13.15 ± 1.41	335.26	P2<0.001**
Range	4-7	5-8	11-16		P3<0.001**
Ferritin (ng/ml)					P1>0.05
Mean ±SD	3738.83 ±3 717.56	2762.13 ± 1524.75	102.25 ± 24.9	42.31	P2<0.001**
Range	400-15900	1050-7000	50-140		P3<0.001**

Standard error (SD), ANOVA F-test (F), *Significant

Table 2. Comparison between studied groups regarding hemoglobin & ferritin level.

The current study found non-significant difference between the studied groups regarding kidney function test (S urea, serum Creatinine and Creatinine clearance) (P>0.05), (Table 3).

Items	Thalassemia major (n=35)	Thalassemia intermediate (n=15)	Control (n=20)	F	P value
Blood urea (mg/dl)					
Mean ±SD	26.17 ± 4.54	27.27 ± 7.23	25.25 ± 5.27	0.59	p>0.05
Range	18-35	18.45	18.35		
Serum creatinine (mg/dl)					
Mean ±SD	0.48 ± 0.1	0.58 ± 0.2	0.45 ± 0.17	4.54	P>0.05
Range	0.34-0.70	0.4-1.2	0.4-0.7		
Creatinine clearance 24h urine (ml/min/1.73m2)					
Mean ±SD	122.67 ± 12.19	120.84 ± 12.06	120.25 ± 7.91	0.34	P>0.05
Range	106.2-145	108-143	110-135		

Standard error (SD), ANOVA F-test (F)

Table 3. Comparison between studied groups regarding mean value of kidney function test|.

The current study found non-significant difference between both types of thalassemia regarding to urine B2 M(P>0.05). and highly positive significant increase in both types of thalassemia in comparing to control (P<0.001), (Table 4, Figure 2). The current study found a significant positive correlation between B2M and age, frequency of transfusion, and serum ferritin (P<0.05). Also, highly significant positive correlation was found between B2M and duration of chelation, serum urea, serum creatinine, Na, K, Ca and Ph (P<0.001). While a significant negative correlation was found between B2M and

Hb, age at start of transfusion (p<0.05), and highly significant negative correlation found between B2M and creatinine Cr 24-hour urine (P<0.001) among the studied patients (Table 5).

	Thalassemia major (n=35)	Thalassemia interme-diate (n=15)	Controls (n=20)	K-test	P value
B2 macroglobulin (µg/l)					P1>0.05
Mean ±SD	106.55±75.75	143.83±50.27	48.45±24.03	17.99	P2<0.001**
Range	1.6-250	60-268.8	8-90		P3<0.001**

Standard error (SD), Kruskal Wallis test (K), *Significant

Table 4. Comparison between studied groups regarding urine B2 macroglobulin.

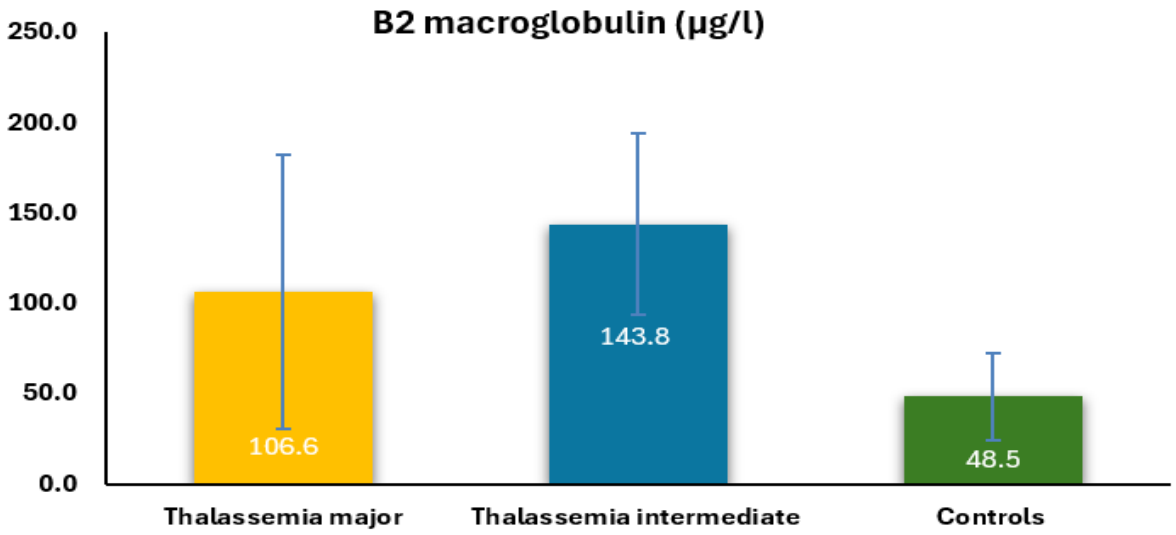

Figure 2. urine B2 macroglobulin distribution among the studied pediatric patients.

Parameters	B2 Thalassemia Major (n=35)		B2 Thalassemia intermediate (n=15)	
	r	P value	r	P value
Age (in years)	0.49	<0.001**	0.13	>0.05
Age at start of transfusion (months)	- 0.35	<0.05*	-0.66	<0.05*
Frequency of transfusion (month)	0.43	<0.05*	0.63	<0.05*
Duration of chelation/year	0.46	<0.001**	0.53	<0.05 *
Hb(g/dl)	-0. 3	<0.05*	-0.3	<0.05**
Serum ferritin (ng/ml)	0.43	<0.05*	-0.07	>0.05
Serum urea (mg/ dl)	0.67	<0.001**	0.77	<0.001**
Serum creatinine (mg/dl)	0.68	<0.001**	0.41	>0.05
Creatinine clearance 24 hour (ml/ min/1.73m2)	-0.60	<0.001**	-0.82	<0.001**
Na (mEq/L)	0.61	<0.001**	0.66	<0.05
K (mEq/L)	0.59	<0.001**	0.31	>0.05
Ca (mg/24 hour)	0.71	<0.001**	0.31	>0.05
Ph (g/24 hour)	0.65	<0.001**	0.47	>0.05

Pearson correlation coefficient (r).

Table 5. Pearson correlation between B2 microglobulin level and other parameters studied.

The current study found urine B2 microglobulin could be use a diagnostic tool for predicting pediatric patients' renal impairment at area under curve 0.75, and sensitivity 94%, specifically 75%, accuracy 73% at level of 160 (µg/l) with positive and negative predictive value 75% and 57% respectively (Table 6).

B2 microglobulin	Area under curve	Cut off value	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV	NPV
	0.75	160	94%	75%	73%	75%	57%

Table 6. Validity of B2 microglobulin levels in detecting cases of renal impairment.

Discussion

In β-thalassemia major (β-TM), the production of beta-globin chains is severely impaired, because both beta-globin genes are mutated. This imbalance of globin-chain synthesis results in ineffective erythropoiesis and severe microcytic hypochromic anemia [6] in which life can only be sustained by regular blood transfusions [7]. The underlying mechanisms for tubulopathy in patients with β-TM include long-standing anemia, chronic hypoxia, iron overload and dose dependent deferoxamine (DFO) toxicity Sumbonnanonda et al., 2008 and [8-10].

Glomerular damage can also occur in these patients due to recurrent infections as thalassemic patients are more prone to infection from repeated blood transfusion and the repeated use of DFO [11]. It appears to be a direct relationship between the duration of the disease and increased renal complications [10]. Also, renal failure is a terminal event in B thalassemia secondary to: cardiorenal syndrome and hepatorenal syndrome [12]. The study was carried out on 50 thalassemic patients, they were divided into 35 TM &15 TI. They were diagnosed as β thalassemia by CBC&HB electrophresis. 20 apparently healthy children were served as controls. they were matched in age, sex and socio-economic standard.

Results of this study showed no significant differences between the studied groups and the controls as regards to age and sex (P>0.05). However, in our patients there was a highly significant decrease in heights in TM (128.49 ± 21.32), TI (135.6 ± 19.19) when compared with controls (137.8 ± 21.1) (p<0.001). It is explained by [13] who reported that the major cause of growth retardation is hypogonadism, hypothyroidism, and probably, impairment of the GH- IGF-1 axis secondary to hemosiderosis of the pituitary gland and liver. Our results agreed with Desanctis, (2002) [14,6,15] who demonstrated significant decrease in the height of thalassemic children due to growth retardation.

Regarding to the results of the age of the start of blood transfusion in our patients, patients with TM were put on regular blood transfusion earlier because of their severe anemia (5.92 ± 3.89 months) that becomes apparent after 6 months of age [15], whereas patients with TI received blood transfusion somewhat later because of their milder symptoms (54.20 ± 27.22 months) [16]. On comparing the number of patients who had splenectomy, no significant difference was detected (P>0.05) between the TM (68.6%) and TI (53.3%). This come in agreement with [17] as both types of B-TM (TM and TI) was exposed to same factors that leads to increase transfusion requirement and the need for splenectomy. Regarding the results of HB, there was a highly significant decrease in the studied groups when compared to the controls (P<0.001) as the anemia was the first presentation in the diagnosis of thalassemia [15,9]. documented that anemia is usually profound when first documented. Before transfusion, Hb concentration was 2.5 to 6.5 g/dl. On comparing the results of HB level between TM (6.37 ± 0.84 g/dl) and TI (6.26 ± 1.03 g/dl) they showed no significant differences (P> 0.05) and significant decrease in Hb level in thalassmic group when compared to controls (13.15 ± 1.41), (P>0.001) and this is in agreement with [8].

As for β2M are low molecular weight protein normally filtered readily at the glomerulus and is totally reabsorbed and degraded by proximal tubular cells of the kidney. In our study, elevation of urinary β2M is sensitive and reliable early marker of tubular dysfunction [18], in TM it was (106.55 ± 75.75), in TI was (162.32 ± 64.04) and in controls (48.45 ± 24.03), there was a highly significant increase in thalassemia group when compared to controls (P<0.001). This comes in agreement with [19,20,18] Also, Hamed and El Melegy, (2010) studied 69 transfusion dependent B- Thalassmia major. They detected a significant elevated excretion of β2M/ Cr. in their patients with and without chelation therapy when compared with control. No significant differences between TM and TI (P>0.05) regarding β2M. This may be explained by the presence of the same contributing factors for the occurrence of renal dysfunction in both TM and TI [21]. reported that under normal conditions, the proximal tubule reabsorbe more than half of the filtered Na, K. So, changes in the reabsorbtion of Na, K may indicate renal tubular dysfunction in our study. In our study, the results of urine electrolytes sodium (Na) in TM were (206.91 ± 97.35), TI (220.07 ± 100.89) and in controls (68.35 ± 28.08), and potassium (K) was in TM (67.39±29.73), TI (72.69 ± 29.61) and in controls (27.1 ± 11.67). In our results, serum ferritin showed a positive significant correlation with age, duration of chelation therapy and frequency of blood transfusion, β2M, phosphorus, (P<0.05) and negative significant correlation with age at start of transfusion (P<0.05) and highly negative significant correlation with

creatinine clearance (P<0.001). This can be explained by frequent blood transfusion. Beta-thassemia patient record, as they start to receive blood transfusion for long –life once they are diagnosed [15], The absence of a physiological iron excretion mechanism leads to uneven accumulation of this metal in various body organs [7].

Regarding S. creatinine, it showed positive significant correlation with potassium (P<0.05) and highly positive significant correlation with age, S urea, B2 microglobulin, sodium, calcium, phosphorus (P<0.001), and highly negative significant correlation with creatinine clearance 24-hour urine (P<0.001), this comes in agreement with (valdislav et al., 2008).

On the current study, urine β2M showed positive significant correlation with age, frequency of transfusion, serum ferritin (P<0.05). As serum ferritin reflects the increased iron overload in the blood which takes part in the occurrence of renal dysfunction, so it is reasonable to find the increased in the level of β2M as a marker of renal dysfunction in our patients, and There is highly positive significant correlation between B2M and (S urea, S Cr) (P<0.001), and highly negative significant correlation between B2M and age at start of transfusion and Cr C This is in accordance with [22-24] and Sadeghi et al., (2010) who stated a similar correlation, and there is highly positive significant correlation between β2M and urine electrolytes (sodium, potassium, calcium, phosphorus) (P<0.001), and this come in agreement with [22,19,18] as both reflect the decreased in the renal function. Elevation of β2M in urine is sensitive and reliable early marker of tubular dysfunction this comes in agreement with [25,26]. In our results there was positive significant correlation between urine level of (Na) with age, ferritin, s urea, S Cr, B2M, and other urine electrolytes(P<0.05), and highly negative significant correlation with Hb and C Cr. This comes in agreement with [18]. To detect early renal dysfunction, the diagnostic efficiency values for the three studied biochemical markers were evaluated. They were affected by the method of estimation of GFR, either by 24 hours urine collection or by using Schwartz formula.

In the current study, the diagnostic efficiency values for the studied biochemical markers was assessed by estimating creatinine clearance using 24 hours urine collection not by Shwartz formula because, Shwartz formula in not used in persons whom heights is affected as it may not reflect the muscle mass, so this method cannot be applied in the thalassemic patients as their heights is retarded [27]. The results showed the best cut off level of urine β2M was 160 µg/l. 22 patients were above this cut-off and 33 below it and none of the control group was above this level. At this level the diagnostic sensitivity was 94%, the diagnostic specificity was 75% the diagnostic accuracy was 73% and the positive predictive value was 75%.

Strength and limitations of the study

This study's strengths include the inclusion of both β-thalassemia major and intermedia patients with age- and sex-matched controls, comprehensive assessment of renal function using conventional and early sensitive markers such as urinary β2-microglobulin and urine electrolytes, and accurate estimation of GFR through 24-hour urine collection rather than the Schwartz formula. Limitations include the relatively small sample size, particularly for thalassemia intermedia, the cross-sectional design which limits assessment of causal relationships, reliance primarily on biochemical markers without imaging or histopathological confirmation, and potential variability in chelation therapy compliance that could affect renal outcomes.

Conclusion

All thalassemia patients will need more proper control of iron overload. Our data indicates that renal impairment is not rare in β thalassemia. Urine β2 microglobulin is a positive sensitive marker of renal tubular dysfunction especially in thalassemic pediatrics patients. Further studies are needed to investigate the role of new chelators in tubular function parameters, such as urine electrolytes and β2M excretion.

Declaration

Consent for publication: All authors have read and revised the manuscript and agreed to its publication.

Availability of data and material: All data supporting the study are presented in the manuscript or available upon request.

Acknowledgments: Not applicable

Authors' information (optional): Not applicable

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