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Original Article

Serum β2-microglobulin as a marker of renal tubular damage in transfusion-dependent β-thalassemia

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Abstract

Background: β-thalassemia major is a hereditary disorder characterized by transfusion-dependent anemia and associated complications. In patients with β-thalassemia major, one of the long-term complications of regular blood transfusion is renal dysfunction. This study aimed to evaluate serum β2-microglobulin as a marker of the severity of renal tubular dysfunction and to examine the clinical factors associated with the severity of renal tubular dysfunction in children with β-thalassemia major.

Methods: This cross-sectional analytical study was conducted on 134 non-diabetic children with β-thalassemia major who attended thalassemia centers in Mazandaran Province, Iran. Data were collected using a structured checklist that included demographic information, laboratory findings, and clinical parameters. The severity of renal tubular dysfunction was assessed using serum β2-microglobulin levels. Glomerular filtration rate was estimated using the revised Schwartz formula. Pearson correlation analysis was used for statistical analysis.

Results: A significant positive correlation was observed between β2-microglobulin levels and age ($r = 0.311$, $p < 0.001$), number of blood transfusions per year ($r = 0.390$, $p < 0.001$), serum creatinine ($r = 0.732$, $p < 0.001$), blood urea nitrogen ($r = 0.715$, $p < 0.001$), and serum ferritin ($r = 0.505$, $p < 0.001$). In contrast, significant negative correlations were found with serum hemoglobin ($r = -0.433$, $p < 0.001$) and creatinine clearance ($r = -0.383$, $p < 0.001$).

Conclusion: Renal tubular dysfunction in children with β-thalassemia major showed significant correlations with age, iron overload, anemia severity, and transfusion frequency. Serum β2-microglobulin may serve as a useful marker for the early detection of tubular damage and may help guide preventive strategies in clinical practice.

Keywords: β-thalassemia major, Pediatric, Renal tubular dysfunction, β2-microglobulin, Iron overload, Biomarker.

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β-thalassemia major is a common autosomal recessive hemoglobinopathy characterized by severely reduced or absent β-globin synthesis (1), causing transfusion-dependent severe anemia from early life (2). The disease has historically shown a high prevalence among native populations in the Middle East, largely attributed to elevated carrier frequencies and the common practice of consanguineous marriage (3), and Iran is recognized as a primary hotspot for the widespread occurrence of β-thalassemia (4). Repeated and routine blood transfusions in β-thalassemia major result in iron overload in organs such as the liver, heart, and kidneys, ultimately causing chronic complications (5, 6). Renal involvement in β-thalassemia major can manifest as tubular and glomerular dysfunction, often asymptomatic at first (6, 7). Research indicates that chronic anemia, hypoxic stress, iron accumulation in tissues, and chelation therapy are key contributors to renal damage (2, 6).

Multiple studies have identified signs of subclinical renal dysfunction in patients with thalassemia. Behairy et al. (8) observed elevated levels of serum cystatin C and β2-microglobulin in children with β-thalassemia major, which were significantly correlated with serum ferritin and decreased creatinine clearance; both cystatin C and β2-microglobulin function as sensitive and specific biomarkers of early renal impairment in children with β-thalassemia major. Similarly, Arman Bilir et al. (9) reported increased urinary retinol-binding protein (RBP) and other tubular biomarkers in asymptomatic individuals with β-thalassemia major. In fact, β2-microglobulin is a low-molecular-weight protein freely filtered by the glomeruli and reabsorbed by the proximal tubules. Elevated urinary β2-microglobulin reflects impaired tubular reabsorption or increased production, making it a sensitive marker of tubular dysfunction (10). In addition, elevated serum β2-microglobulin is also recognized as a sensitive marker of tubular dysfunction (11). Nevertheless, comprehensive assessments of the association between the severity of tubular dysfunction and underlying clinical variables, such as hemoglobin concentration, serum ferritin, creatinine, urea, transfusion burden, and creatinine clearance, remain scarce. Because renal impairment in patients with thalassemia may progress insidiously and predispose them to chronic kidney disease in adulthood, early identification of contributory risk factors is critical for implementing targeted screening and preventive strategies.

The present study therefore aimed to evaluate serum β2-microglobulin as the primary marker of renal tubular dysfunction severity and to examine its relationship with key clinical and biochemical parameters, including hemoglobin concentration, serum ferritin, creatinine, blood urea nitrogen, transfusion frequency, and creatinine clearance in children with transfusion-dependent β-thalassemia major.

Methods

Study design: This analytical cross-sectional study was conducted on 134 pediatric patients with β-thalassemia major aged 1-16 years, who were referred to thalassemia centers across Mazandaran Province, Iran, during 2021 and 2022. Sample size was calculated based on a previous study by Behairy et al. (8), assuming a correlation coefficient of 0.4, with 95% confidence and 80% power, yielding 134 participants. Sampling was performed using a convenience sampling method. The study aimed to investigate factors associated with the severity of renal tubular dysfunction in these patients.

Inclusion/exclusion criteria: Eligible participants were non-diabetic children with a confirmed diagnosis of β-thalassemia major who were under regular care in thalassemia centers and whose parents signed an informed consent form. Exclusion criteria included a history of known renal disease, urinary tract infection, kidney stones, vesicoureteral reflux, hydronephrosis, immune disorders, malignancies, or diabetes mellitus. Patients receiving nephrotoxic medications other than iron chelators were also excluded.

Data and sample collection: Data were collected using a standardized checklist. Clinical data and laboratory measurements were obtained exactly one week after the most recent blood transfusion. This timing was chosen to allow stabilization of hemoglobin and ferritin levels and to minimize the confounding effects of immediate post-transfusion fluctuations, thereby reducing potential bias. Parameters assessed included serum levels of β2-microglobulin, ferritin, hemoglobin, creatinine, blood urea nitrogen (BUN), and urinary creatinine clearance. In addition, data regarding the type and regimen of iron chelation therapy (deferoxamine or deferasirox) were recorded for each participant. Serum β2-microglobulin was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit. The severity of renal tubular dysfunction was classified according to serum β2-microglobulin levels as follows: normal (<2 mg/L), mild dysfunction (2–3.5 mg/L), moderate dysfunction (3.5–5 mg/L), and severe dysfunction (>5 mg/L). These cut-off thresholds were adapted from previously published literature on β2-microglobulin-based renal assessment in pediatric thalassemia populations (8, 11). Glomerular filtration rate was estimated using Schwartz formula: eGFR (mL/min/1.73 m²) = 0.413 × height (cm) / serum creatinine (mg/dL), for pediatric patients aged 1–16 years (12). Given the well-recognized age-dependent variation in serum creatinine reference ranges in the pediatric population, all creatinine values were interpreted in the context of age- and sex-specific normative ranges established for children, rather than applying adult reference intervals.

Statistical analysis: Statistical analyses were performed using SPSS Version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation for continuous variables and frequencies for categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess normality. Pearson correlation coefficients were calculated to assess relationships between serum β2-microglobulin and clinical/laboratory parameters. A p-value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics: A total of 134 children with β-thalassemia major were enrolled in this study, including 77 (57.5%) males and 57 (42.5%) females, with a mean age of 13.41±2.70 years. The mean annual number of blood transfusions was 13.89±1.13, reflecting regular transfusion dependency. The mean hemoglobin concentration was 9.44±0.36 g/dL, indicating persistent anemia despite ongoing transfusion therapy. Serum ferritin levels averaged 1197.21±381.51 ng/mL, confirming substantial iron overload among participants.

Renal function parameters: Renal function indices revealed a mean serum creatinine level of 0.75±0.33 mg/dL, a BUN of 14.25±5.30 mmol/L, and an average creatinine clearance of 104.02±22.78 mL/min/1.73 m². The mean serum β2-microglobulin concentration was 1.15±0.58 mg/L, serving as an early indicator of tubular dysfunction.

Correlation between β2-microglobulin and laboratory variables: To evaluate the associations between β2-microglobulin and other clinical and biochemical parameters, Pearson correlation analysis was performed.

Positive correlations: A strong positive correlation was observed between β2-microglobulin and serum creatinine ($r = 0.732$, $p < 0.001$) as well as BUN ($r = 0.715$, $p < 0.001$), suggesting that increasing β2-microglobulin levels parallel early renal impairment.

Additionally, moderate positive correlations were detected with serum ferritin ($r = 0.505$, $p < 0.001$), frequency of blood transfusions ($r = 0.390$, $p < 0.001$), and age ($r = 0.311$, $p < 0.001$), indicating that iron overload, transfusion burden, and disease duration contribute to progressive renal tubular injury.

Negative correlations: Moderate negative correlations were found between β2-microglobulin and hemoglobin concentration ($r = -0.433$, $p < 0.001$) as well as creatinine clearance ($r = -0.383$, $p < 0.001$), reflecting the adverse influence of chronic anemia and declining glomerular filtration on tubular function (table 1).

Table 1. Summary of key clinical and laboratory findings and their correlation with β2-microglobulin

Variable	Mean±SD	Correlation with β2-MG (r)	P-value
Serum Creatinine (mg/dL)	0.75±0.33	+0.732	<0.001
Blood Urea Nitrogen* (mmol/L)	14.25±5.30	+0.715	<0.001
Serum Ferritin (ng/mL)	1197.21±381.51	+0.505	<0.001
Hemoglobin (g/dL)	9.44±0.36	−0.433	<0.001
Creatinine Clearance (mL/min/1.73 m²)	104.02±22.78	−0.383	<0.001
Blood Transfusions per Year	13.89±1.13	+0.390	<0.001
Age (years)	13.41±2.70	+0.311	<0.001

Abbreviations: β2-MG = β2-microglobulin; SD = standard deviation.

Discussion

In this cross-sectional study of 134 pediatric patients with β-thalassemia major, we employed serum β2-microglobulin a low-molecular-weight protein sensitive to proximal tubular dysfunction as the primary index of renal tubular injury severity. The findings build upon a growing body of evidence suggesting that renal involvement in thalassemia is not merely a late-stage complication but a clinically silent and progressive process that may begin years before overt renal failure becomes detectable. Importantly, this study provides a comprehensive simultaneous evaluation of multiple disease burden indicators including iron overload, anemia, transfusion frequency, and glomerular filtration in a well-characterized Iranian pediatric cohort, a population with one of the highest global burdens of β-thalassemia. By quantifying the associations between β2-microglobulin and these parameters, our results contribute contextually specific and clinically actionable data to the existing literature on thalassemic nephropathy.

One of the most striking findings was the strong positive correlation between β2-microglobulin and serum creatinine and BUN. These correlations indicate that as glomerular function begins to decline, tubular dysfunction, as reflected by β2-microglobulin, becomes more prominent. However, since β2-microglobulin can increase even when glomerular function is preserved, its elevation may reflect early and subclinical tubular damage before overt renal failure is

evident. These results align with prior reports. Behairy et al. (8) similarly observed elevated β2-microglobulin in children with β-thalassemia major, which correlated positively with ferritin and serum urea and negatively with creatinine clearance, supporting its utility as a sensitive early biomarker of renal injury. The negative correlation with creatinine clearance is particularly important, as it highlights the relationship between early tubular dysfunction and declining overall renal function. Creatinine clearance is a surrogate for glomerular filtration rate (GFR), and its decrease in conjunction with elevated β2-microglobulin suggests that tubular injury may eventually progress to glomerular involvement if not identified and addressed early. We also observed that older age and lower hemoglobin were associated with tubular damage, likely reflecting cumulative transfusion exposure and chronic anemia. Anemia and the resulting chronic hypoxia may also contribute to the activation of oxidative stress, lipid peroxidation, and subsequent tubular dysfunction. Moreover, hypoxia itself can induce the differentiation of tubular cells into myofibroblasts, while simultaneously activating fibroblasts, altering extracellular matrix metabolism in renal cells, and promoting obliteration of the peritubular capillaries (6). Other investigators have similarly reported proximal tubular dysfunction (e.g., proteinuria, hypercalciuria, β2-microglobulinuria) in heavily transfused thalassemic children (13).

We identified elevated serum ferritin as one of the strongest correlates of dysfunction severity, supporting the hypothesis that iron-mediated tubular toxicity plays a central role in thalassemic nephropathy through mitochondrial dysfunction, generation of free radicals, and ultimately, cell death (6, 14, 15). Sadeghi-Bojd et al. found that 95% of patients with major thalassemia had iron overload and many had biochemical evidence of tubulopathy (13). Furthermore, our study found that the frequency of annual blood transfusions was positively correlated with β2-microglobulin, reflecting the cumulative iron burden from transfused red cells. The role of iron chelation therapy in renal toxicity warrants specific consideration. Although our study was not designed to compare chelation regimens, the specific type, duration, and dosage of chelation therapy, most commonly deferoxamine (subcutaneous) or deferasirox (oral) in Iranian thalassemia centers, may independently influence renal tubular function. Deferoxamine-associated nephrotoxicity has been described in prior literature (14), while oral deferasirox is known to have direct nephrotoxic potential even at therapeutic doses (14). We recorded chelation regimen data for all participants; however, formal comparative analysis of chelation type was beyond the scope of this preliminary study. Future studies with adequate power for stratified analysis are warranted to disentangle the respective contributions of iron overload and chelation nephrotoxicity to tubular dysfunction in this population. Monitoring both serum β2-microglobulin and ferritin levels in tandem may offer a more complete picture of renal status in thalassemic patients. Interestingly, patient age was also positively correlated with β2-microglobulin. This may reflect the cumulative effects of disease duration, iron exposure, and transfusion burden. Older children are more likely to have experienced longer-standing oxidative and hypoxic stress and thus are more vulnerable to progressive renal damage. Shaalan et al. (16) reported that children with β-thalassemia major had abnormal tubular and glomerular markers, particularly in association with older age, high ferritin levels, and deferoxamine therapy.

Taken together, these findings strongly support the notion that renal tubular dysfunction is not merely a secondary or late-stage complication of β-thalassemia major, but rather a frequent and insidious aspect of the disease, beginning early and progressing silently. The use of β2-microglobulin as a screening tool for early tubular injury is both practical and informative, especially when routine serum creatinine and urea values remain within normal limits. From a clinical standpoint, early identification of tubular damage could prompt more aggressive iron chelation strategies, tighter transfusion control, and closer renal monitoring, potentially delaying or preventing long-term renal complications. This is particularly critical in pediatric patients, where early intervention may preserve renal function and improve long-term outcomes. While our study is strengthened by its sample size and comprehensive analysis of biochemical parameters, it is not without limitations.

The cross-sectional design restricts our ability to infer causality or assess disease progression. Second, only serum β2-microglobulin was measured; urinary β2-microglobulin, which may provide even greater sensitivity for proximal tubular dysfunction by directly reflecting tubular reabsorptive capacity, was not assessed and should be incorporated in future studies. Third, although chelation regimen data were recorded, the specific impact of different chelation agents and dosages on renal function was not formally analyzed as a separate variable; future studies should address this confounding factor through stratified or multivariate analyses. Fourth, given the cross-sectional and exploratory nature of this investigation, we performed Pearson correlation analysis as the primary statistical approach to quantify bivariate associations. Multivariate

regression analysis was not performed owing to the limited sample size and non-normal distribution of some covariates; however, future studies with larger cohorts should include multivariate models to simultaneously adjust for confounding variables such as age, chelation regimen, and transfusion frequency. In summary, our results underscore the importance of proactive renal evaluation in children with β-thalassemia major. Serum β2-microglobulin appears to be a valuable and feasible marker for early tubular injury and is significantly associated with multiple clinical risk factors, including anemia severity, iron overload, and decreased creatinine clearance. Longitudinal studies are needed to validate its prognostic value and to determine whether early detection and intervention can meaningfully alter the renal trajectory in this vulnerable population. Renal tubular dysfunction is a significant and under-recognized complication in pediatric patients with β-thalassemia major. In this study, elevated serum β2-microglobulin levels used as a marker of tubular injury were strongly associated with indicators of iron overload, chronic anemia, and renal stress, including higher serum creatinine, BUN, ferritin levels, increased transfusion frequency, and advancing age. Conversely, lower hemoglobin levels and decreased creatinine clearance were significantly linked with more severe tubular dysfunction. These findings emphasize the importance of early renal monitoring in thalassemia care. Routine assessment of β2-microglobulin, along with hematologic and iron status parameters, may help in the early detection of subclinical renal impairment and guide timely interventions. Integrating renal protective strategies into routine thalassemia management may mitigate long-term renal damage and improve quality of life in this vulnerable population. Future longitudinal studies are recommended to assess the progression of renal injury over time and to evaluate the prognostic value of β2-microglobulin in larger and more diverse thalassemic populations.

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Ethics approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Babol University of Medical Sciences (Ethics Code: IR.MUBABOL.REC.1401.103). Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment.

Conflict of interest: The authors declare that they have no conflicts of interest.

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