

Evaluation of Renal Function Biomarkers in Yemeni Patients with Transfusion-Dependent β -Thalassemia

Boshra Al-absi^{*1,2}, Elham Qateena¹, Nada Anam¹,
Rahma Noman¹, Raghad AL-shmahi¹, Amjed AL-asbahi¹

¹Department of Laboratory Medicine, Faculty of Medicine and Health Sciences, Ar-Rasheed Smart University, Sana'a, Yemen

²Department of Hematology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen

*Corresponding Author:

E-mail: b.alabsi@su.edu.ye

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Abstract

β -thalassemia is an inherited blood disorder characterized by a reduction in β -globin chain synthesis. Renal biomarkers may change in patients with transfusion-dependent β -thalassemia (TDT), a severe form of β -thalassemia, due to iron overload and chelation therapy. This study aimed to evaluate the renal function biomarkers (urea, creatinine, and eGFR) in TDT Yemeni patients. Eighty subjects were enrolled in this study, aged 2-29 years. These subjects encompassed 40 TDT patients and 40 healthy controls. Blood samples were examined for urea, creatinine, complete blood count, and iron profile using automated analyzers. Results showed that urea and creatinine levels were significantly decreased in patients. In contrast, estimated glomerular filtration rate (eGFR) was significantly higher in TDT patients. Serum iron levels and transferrin saturation were significantly elevated in patients. Urea was negatively correlated with age ($r = -0.345$; $p = 0.03$) and positively correlated with RBC count ($r = 0.339$; $p = 0.01$), whereas creatinine was positively correlated with age ($r = 0.470$, $p = 0.002$) and negatively correlated with MCHC ($r = -0.405$, $p = 0.01$). Further studies, including early renal biomarkers such as urinary β_2 -microglobulin and the urine calcium-to-creatinine ratio, are required to confirm the presence of subclinical kidney injury in TDT patients.

Keywords: Thalassemia, transfusion-dependent, renal markers, iron overload, Yemen

تقييم المؤشرات الحيوية لوظائف الكلى لدى المرضى اليمنيين المصابين بثلاسيميا بيتا المعتمدين على نقل الدم

بشرى العبيسي^{*1,2}، إلهام قاتينا¹، ندى أنام¹،
رحمة نومان¹، رغد الشماحي¹، أمجد الأسبهي¹

¹قسم الطب المخبري، كلية الطب والعلوم الصحية، جامعة الرشيد الذكية، صنعاء، اليمن

²قسم أمراض الدم، كلية الطب والعلوم الصحية، جامعة صنعاء، صنعاء، اليمن

*المؤلف المراسل:

الإيميل: b.alabsi@su.edu.ye

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الملخص

تُعد ثلاسيميا بيتا اضطراباً وراثياً في الدم يتميز بنقص في تخليق سلاسل بيتا جلوبيين. وقد تتغير المؤشرات الحيوية الكلوية لدى المرضى المصابين بثلاسيميا بيتا المعتمدين على نقل الدم (TDT) - وهي شكل حاد من ثلاسيميا بيتا - نتيجة لفرط حمل الحديد والعلاج بالاستخلاب. هدفت هذه الدراسة إلى تقييم المؤشرات الحيوية لوظائف الكلى (اليوريا، والكرياتينين، ومعدل الترشيح الكبيبي المقدّر [eGFR]) لدى المرضى اليمنيين المصابين بثلاسيميا بيتا المعتمدين على نقل الدم. شملت الدراسة ثمانين مشاركاً تراوحت أعمارهم بين 2 و 29 عاماً، حيث ضمت 40 مريضاً بثلاسيميا بيتا المعتمدين على نقل الدم و 40 شخصاً سليماً كمجموعة ضابطة. تم فحص عينات الدم لتحديد مستويات اليوريا، والكرياتينين، وتعداد الدم الكامل، ومؤشرات الحديد (Iron profile) باستخدام أجهزة تحليل آلية. أظهرت النتائج انخفاضاً معنوياً في مستويات اليوريا والكرياتينين لدى المرضى. وفي المقابل، كان معدل الترشيح الكبيبي المقدّر (eGFR) المحسوب أعلى بكثير لدى مرضى ثلاسيميا بيتا المعتمدين على نقل الدم. كما ارتفعت مستويات حديد المصل وترشيح الترانسفيرين بشكل ملحوظ لدى المرضى. ارتبطت مستويات اليوريا ارتباطاً عكسياً (سلبياً) بالعمر ($r = -0.345$, $p = 0.03$) وطردياً (إيجابياً) مع تعداد خلايا الدم الحمراء ($r = 0.339$, $p = 0.01$)، في حين ارتبط الكرياتينين ارتباطاً طردياً بالعمر ($r = 0.470$, $p = 0.002$) وعكسياً مع تركيز الهيموجلوبين في الكرية (MCHC) ($r = -0.405$, $p = 0.01$). ثمة حاجة إلى إجراء المزيد من الدراسات، بما في ذلك تقييم المؤشرات الحيوية الكلوية المبكرة مثل الببتا 2-ميكروجلوبولين البولي ونسبة الكالسيوم إلى الكرياتينين في البول، لتأكيد وجود إصابة كلوية دون سريرية لدى مرضى ثلاسيميا بيتا المعتمدين على نقل الدم.

الكلمات المفتاحية: ثلاسيميا، المعتمد على نقل الدم، علامات الكلى، زيادة الحديد، اليمن

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1. Introduction

Thalassemia is a common inherited blood disorder marked by α - and β -globin chain imbalance. β -thalassemia (β -thal) results from mutations in the β -globin gene causing deficient β -chain production, which in turn results in excess α -chains that precipitate with red cells leading to hemolysis and ineffective erythropoiesis. β -thalassemia major (β -TM) is the severe type in which patient survival depends on regular blood transfusions, thus developing iron overload (every patient with β -TM is transfusion-dependent, but not every transfusion-dependent β -thalassemia (TDT) patient has β -TM) [1].

Although β -TM affects bone marrow, its impact extends to various organs, including kidneys. Chronic hemolytic anemia, iron overload, and chelation therapy may lead to kidney dysfunction in TDT patients [2]. In the first stages of renal disease, hyperfiltration of glomeruli may occur, which can develop into kidney damage and proteinuria. Oxidative stress and renal injury may arise from increased iron deposition [3]. Tubular dysfunction includes reduced urine-concentration, tubular acidosis, and losses of potassium, phosphate, and magnesium, which are caused by chronic hypoxia and iron overload in renal tubules [4]. Repeated transfusions worsen tissue iron accumulation, which is toxic to the kidneys. Moreover, iron chelators such as deferoxamine, deferasirox, and deferiprone may cause renal toxicity [5].

In Yemen, the prevalence of the β -thal trait is high (4.4%) suggesting this homozygous β -thal disease constitute a health burden in the country [6]. In low-income countries, like Yemen, TDT patients have difficulties obtaining adequate and suitable blood units, iron chelation therapy, and routine monitoring of their kidney functions. These challenges increase the risks of developing renal dysfunction [7]. Understanding risk factors and complications of kidney dysfunction will help

develop strategies for detection and prevention of renal disorders in these patients. Consequently, this study is designed to assess renal biomarkers by measuring urea and creatinine, and calculating eGFR in TDT patients.

2. Materials and Methods

This case-control study was conducted at the Yemen Society for Thalassemia and Genetic Blood Disorder (YSTH) Center in Sana'a City from October to November 2024. Eighty participants were included: 40 TDT patients and 40 age- and sex-matched healthy controls. The OpenEpi software, version 3 (CDC, Atlanta, USA) was used to calculate the sample size at a 95% confidence level and 80% power, according to a previous report by Tantawy et al. [8]. Body mass index (BMI) was calculated for each participant. Patients with kidney failure or those who had received a blood transfusion within the previous three weeks were excluded.

2.1. Sample Collection and Testing

Venous blood samples (10 mL) were collected from each individual by venipuncture. Samples were transferred into ethylenediaminetetra acetic acid (EDTA) tubes for hematological analysis and plain tubes for serum separation. Complete blood count (CBC) was examined by Sysmex KX-21N Hematology analyzer (Sysmex Corporation, Japan). Levels of urea, creatinine, iron, total iron-binding capacity (TIBC), and unsaturated iron-binding capacity (UIBC) were analyzed using a Beckman Coulter AU480 automated analyzer (Danaher Corporation, USA). The estimated glomerular filtration rate (eGFR) is a widely used measure of kidney function and it plays an important role in the detection and monitoring of chronic kidney disease (CKD). CKiD U25 Equation (2021) is used for individuals aged 1 to 25 years [9]. The 2021 CKD-EPI creatinine equation is used for individuals aged 26–29 [10].

Transferrin saturation was calculated using the following equation [11]:

$$\text{Transferrin saturation(\%)} = (\text{Serum iron} \div \text{TIBC}) \times 100$$

2.2. Statistical Analysis

Data were processed using the Statistical Package for the Social Sciences (SPSS 25.0, LEAD Technologies, Inc., Chicago, USA). Normally distributed variables were presented as mean $\pm$ SD standard deviation, while geometric mean with 95% confidence intervals was used for non-normally distributed parameters. Independent-samples t-test was applied to compare mean differences. The relationship between kidney function biomarkers (urea and creatinine), iron profiles, and hematological parameters was evaluated using Pearson's correlation coefficient. Significant differences were considered if the p-value was <0.05 .

3. Results

This study enrolled a total of 80 subjects aged between 2 and 29 years old, of whom 40 had TDT and 40 controls. The cohort consisted of 52 males and 28 females.

Demographic and hematologic parameters for both TDT patients and controls are presented in Table 1. Hemoglobin (Hb), red blood cell (RBC) count, hematocrit (Hct), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were significantly lower in the patient group compared to controls ($p < 0.05$). Conversely, red cell distribution width-coefficient of variation (RDW-CV) was significantly higher in thalassemia patients ($p < 0.0001$). White blood cell (WBC) count was non-significantly higher in the patients than in the controls ($p = 0.08$). No significant differences were observed between patients and controls in terms of age, Body Mass Index (BMI), mean corpuscular volume (MCV), and platelets (PLT).

Table 1. Demographic and hematologic parameters of TDT patients and controls

Parameters	Thalassemia patients (n = 40)	Control (n = 40)	p-value
	Mean $\pm$ SD	Mean $\pm$ SD	
Age (Years)	10.8 $\pm$ 5.5	11.6 $\pm$ 6.1	0.51
BMI	17.6 $\pm$ 6.4	19.9 $\pm$ 6.5	0.12
Hb (g/dL)	7.8 $\pm$ 1.2	13.9 $\pm$ 1.4	$< 0.0001^+$
RBCs ($\times 10^{12}$ /L)	3.1 $\pm$ 0.5	5.2 $\pm$ 0.6	$< 0.0001^+$
Hct (%)	23.7 $\pm$ 3.6	40.6 $\pm$ 4.2	$< 0.0001^+$
MCV (fL)	77.4 $\pm$ 6.5	79 $\pm$ 6.6	0.29
MCH (pg)	25.6 $\pm$ 2.8	27.1 $\pm$ 2.6	0.02^+
MCHC (g/dL)	33.1 $\pm$ 1.5	34.3 $\pm$ 1	$< 0.0001^+$
RDW-CV (%)	20 $\pm$ 5.2	13.9 $\pm$ 0.9	$< 0.0001^+$
WBCs* ($\times 10^9$ /L)	8.1 (6.9–9.5)	6.9 (6.3–7.5)	0.08
PLTs* ($\times 10^9$ /L)	324 (269–389)	309 (295–331)	0.79

* Data are presented as geometric mean (95% confidence interval) evaluated by Independent-Samples t-test.

⁺ Significant level $p < 0.05$.

The comparison of the TDT patients with the healthy controls drawn in Table 2 revealed significantly higher serum iron levels and transferrin saturation in patients ($p < 0.0001$), while TIBC and UIBC were significantly higher in healthy controls ($p < 0.0001$ and $p < 0.0001$, respectively).

Furthermore, Table 2 showed that serum urea and creatinine levels were significantly lower in thalassemia patients compared to controls ($p = 0.003$ and $p < 0.0001$,

respectively). The eGFR was significantly higher in patients compared to controls ($p < 0.0001$).

Table 3 revealed that urea was negatively correlated with age ($r = -0.345$, $p = 0.03$) but positively correlated with RBC count ($r = 0.339$, $p = 0.01$). On the other hand, creatinine was positively correlated with age ($r = 0.470$, $p = 0.002$) and negatively correlated with MCHC ($r = -0.405$, $p = 0.01$). No correlation was found between eGFR and the other parameters.

Table 2. Iron profile and kidney function tests of TDT patients and controls

Parameters	Thalassemia patients (n = 40) (mean $\pm$ SD)	Control (n = 40) (mean $\pm$ SD)	p-value
Serum iron ($\mu\text{mol/L}$)	33.4 $\pm$ 15.6	13.7 $\pm$ 5.1	< 0.0001 ⁺
TIBC ($\mu\text{mol/L}$)	45.8 $\pm$ 16.3	64.1 $\pm$ 6.8	< 0.0001 ⁺
UIBC ($\mu\text{mol/L}$)	12.1 $\pm$ 7	50.4 $\pm$ 8.4	< 0.0001 ⁺
Transferrin saturation (%)	72 $\pm$ 15	22 $\pm$ 9	< 0.0001 ⁺
Urea (mmol/L)	3.71 $\pm$ 1.1	4.4 $\pm$ 1	0.003 ⁺
Creatinine ($\mu\text{mol/L}$)	22.7 $\pm$ 8	45 $\pm$ 17.8	< 0.0001 ⁺
eGFR (mL/min/1.73m ²)	197 $\pm$ 56	113 $\pm$ 26	< 0.0001 ⁺

Data are presented as mean $\pm$ SD evaluated by Independent-Samples t-test. ⁺ Significant level $p < 0.05$.

4. Discussion

β -thalassemia is an inherited disorder characterized by a deficiency in β -globin chain production, leading to microcytic hypochromic anemia [12, 13]. Extravascular hemolysis results from erythrocyte fragility, and both extravascular hemolysis and ineffective erythropoiesis can contribute to anemia in β -thalassemia patients [14, 15]. β -thalassemia is also associated with metabolic irregularities, excessive iron storage in various organs, chronic hypoxia, and cellular injury [16]. The current study aimed to investigate kidney function in TDT patients compared to healthy subjects.

This study showed that urea and creatinine levels were within the reference range but significantly decreased in the patients compared to the control. These findings align

with a previous study demonstrating significantly reduced plasma urea and creatinine in thalassemia patients compared to healthy subjects [17]. Conversely, other studies reported no significant differences in urea and creatinine levels within thalassemia patients [18, 19]. Patients' mean age in the current study was 10 years; however, mild dysfunction of renal tubules and reduced glomerular filtration rate have been observed in old patients suffering from β -thalassemia major, α -thalassemia, and hemoglobin E/ β -thalassemia [20, 21]. Tubular defect in β -thalassemia has been linked to several factors, including chronic anemia with hypoxemia, intravascular and extravascular destruction of RBCs, long-term blood transfusions, iron accumulation, and desferrioxamine toxicity [22–25]. Furthermore, the decrease in creatinine levels

may be associated with a lower BMI due to developmental delays and reduced muscle mass in β -thalassemia patients [26, 27]. The findings of the current study revealed that eGFR was significantly higher in the patient group. This result contradicts a 2023 meta-analysis of 15 studies, which found GFR was higher in healthy controls than in patients with β -thalassemia major [28]. On the other hand, Hassanein et al. [29] reported higher eGFR in thalassemia major cohorts. Hyperdynamic circulation in thalassemia, resulting from chronic anemia, increases renal plasma flow, leading to glomerular hyperfiltration [29]. The eGFR is overestimated by various serum creatinine-based equations due to low creatinine levels in TDT patients. This can be attributed to the fact that urinary excretion of creatinine is equal to creatinine production in healthy individuals, as most creatinine is produced by muscles, whereas the lower creatinine clearance in TDT patients indicates decreased production by their muscles [30].

In this study, Hb, RBCs, Hct, MCH, and MCHC were significantly lower in thalassemia patients. In contrast, RDW-CV was significantly higher in thalassemia patients compared to controls. These findings are consistent with previous studies reporting decreased Hb, RBCs, and RBC indices in thalassemia patients [31, 32]. These reductions can be attributed to the chronic hemolytic anemia characteristic of β -thalassemia, which leads to a constant drop in hemoglobin, erythrocyte count, and specific red blood cell indices [33]. The elevated RDW-CV indicates anisocytosis due to erythrocyte fragments, normoblasts, microspherocytes, and microcytic erythrocytes [34].

Conversely, platelet and white blood cell counts were non-significantly increased in patients; they remained within the normal reference range. This result is consistent with previous studies [32, 35]. Increased activity of the immune system in patients receiving

Table 3. Pearson Correlation Coefficient between renal biomarkers and hematological and iron profile parameters of TDT patients (n=40)

Parameter	Age	BMI	Hb	RBCs	Hct	MCV	MCH	MCHC	RDW-CV	WBCs	PLT	Serum iron	Transferrin saturation	TIBC	UIBC
Urea	-0.345*	0.147	0.313	0.339*	0.289	-0.227	-0.153	0.046	0.067	-0.062	-0.028	-0.144	-0.231	-0.023	0.21
Creatinine	0.470*	-0.162	-0.034	0.162	0.093	-0.143	-0.278	-0.405*	0.273	-0.031	-0.028	0.198	0.027	0.239	0.095
eGFR	0.171	-0.036	0.004	-0.162	-0.039	0.258	0.261	0.145	0.006	-0.048	0.043	0.048	0.109	-0.013	-0.102

*Correlation is significant at the level of less than 0.05.

frequent blood units from different donors, often accompanied by febrile reactions, may explain the elevations in WBC and platelet counts [36, 37]. Importantly, most thalassemia patients (n= 33) in the current study had not undergone splenectomy, leading to normal leukocyte and platelet counts. Increased susceptibility to infections and septic complications was associated with splenectomy, leading to higher morbidity and mortality compared to non-splenectomized patients [38, 39].

In the current study, UIBC and TIBC were significantly lower in β -thalassemia patients. This result is consistent with previous reports [40, 41]. Concurrently, an increase in serum iron levels and transferrin saturation has been observed in β -thalassemia patients, which is supported by several other studies [42–44]. In β -thalassemia, the reduction of β -globin chains leads to the deposition of α -globin chains. The excess amount of these α -globin chains is a main contributor to cellular oxidative stress and erythroid cell damage, and the resulting ineffective erythropoiesis stimulates iron overload [45, 46]. Moreover, iron overload is attributed to chronic blood transfusions in these patients [47]. TIBC and UIBC quantify the capacity of the body to bind and transport iron by transferrin [48]. In beta-thalassemia major, there is increased iron absorption in response to ineffective erythropoiesis, while the diminished production of beta-globin chains results in the ineffective utilization of absorbed iron, leading to accumulation of unbound iron in the blood [49]. This excess iron can induce tissue damage and other complications [50]. No previous studies have supported the findings of the present study regarding the negative relationship between urea and age or the positive association of urea with RBC count in transfusion-dependent β -thalassemia patients. Furthermore, no evidence was found for a positive correlation between creatinine level, age, and MCHC.

The limitations of the present study include a small sample size, the lack of serum ferritin measurement, and a short study duration. Further longitudinal research is recommended to evaluate renal function in patients with transfusion-dependent β -thalassemia.

5. Conclusion

This study revealed that kidney function markers (urea and creatinine) were low in TDT patients, while serum iron and transferrin saturation were significantly higher. TIBC and UIBC levels in TDT patients were lower than those in healthy controls were. Further studies including investigation of early renal biomarkers such as urinary β 2 microglobulin and urine calcium to creatinine ratio are required to confirm the presence of subclinical kidney injury in TDT patients.

Ethical Approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Ar-Rasheed Smart University, Sana'a, Yemen (Approval No. REC-ARSU-001).

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Data Availability

The data are available from the corresponding author upon request.

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