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Kidney Function in Patients With Different Variants of Beta-Thalassemia

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Introduction. Renal involvement is a rare complication of β-thalassemia. Both tubular and glomerular dysfunction might occur in these patients. The aim of this study was to evaluate and compare kidney function in the major, intermedia, and minor variants of β-thalassemia.

Materials and Methods. Renal tubular and glomerular function of 72 patients with β-thalassemia (25 major, 23 intermedia, and 24 minor) were evaluated. Patients older than 40 years and those with chronic kidney disease, diabetes mellitus, congestive heart failure, associated infections, congenital anomalies of the kidney and urinary tract were excluded. Blood and urine samples were collected electrolytes and markers of kidney function.

Results. Mean age at the time of study was significantly higher in the minor group. The majority of patients with thalassemia major were males. Hematuria and pyuria occurred in 4% to 8% of the patients. Serum level of all variables were within normal limits, with no significant difference between the three groups. Glomerular filtration rate was nonsignificantly higher in the major and intermedia groups, compared to the minor variant. A significantly lower urine phosphorus and uric acid excretion was noted with the minor variant. Urine phosphorus and uric acid excretion increased more frequently in the major and intermedia groups.

Conclusions. Tubular and glomerular functions appear to be well preserved in all variants of β-thalassemia.

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INTRODUCTION

Thalassemia is one of the most common hereditary hematologic disorders, characterized by severe disturbances in beta chain hemoglobin synthesis.[1] Recent advances in the medical care of these patients have improved survival rate and increased recognition of unusual complications, such as renal involvement.[2] Kidney dysfunction signs such as increased renal blood flow, urine concentration defect, and renal tubular acidosis have been reported in patients with thalassemia, since 1975.[3] However, renal involvement is an uncommon complication of β-thalassemia with subclinical and nonsignificant manifestations.[4-6] Mild tubular dysfunction and decreased glomerular filtration rate (GFR) have been described in older patients with α-thalassemia, β-thalassemia major, and hemoglobin E/β-thalassemia.[7] Prolonged anemia with chronic hypoxemia, intravascular and extravascular hemolysis, chronic and high-intensity transfusion, iron overload, and prolonged high-dose deferoxamine treatment are the main causes of kidney dysfunction in these patients.[2,8] In addition, hepatitis B, hepatitis C, human immunodeficiency

virus infection, and iron-induced cardiac or hepatic dysfunction are other rare causes of decreased kidney function.[9] Based on asymptomatic kidney dysfunction, regular screening of kidney function has been suggested in high-risk thalassemic patients with diabetes mellitus, hypertension, proteinuria, and a GFR less than 60 mL/min/1.73 m^2, as well as older patients, in order to detect early renal involvement and to prevent incipient kidney impairment.[10]

There are limited reports concerning the assessment of kidney function in different types of β-thalassemia. The aim of this study was to compare renal tubular and glomerular functions in 3 different variants of β-thalassemia for the early prediction of kidney dysfunction in these patients.

MATERIALS AND METHODS

This cross-sectional study included 72 patients with 3 different variants of hypochromic microcytic β-thalassemic anemia (25 major, 24 minor, and 23 intermedia) admitted to the pediatric hematology clinic of Aliasghar children's hospital from 2015 to 2016. The study protocol was in accordance to the Helsinki Declaration and was approved by the institutional ethics committee. Informed consent was obtained from all participants. Patients with pure β-thalassemia who had close regular follow-up visits were included in this study. Patients with clinical or laboratory evidence of kidney dysfunction, diabetes mellitus, congestive heart failure, hepatic impairment, thyroid disorder, infection, associated hemoglobinopathies, congenital anomalies of the kidney and urinary tract, glomerulonephritis, and an age over 40 years were excluded.

Major thalassemia was defined as hypochromic microcytic anemia with a hemoglobin F level greater than 90%, and the need for transfusion every 3 to 4 weeks. The intermedia variant was considered as anemia identified at 3 to 4 years old, with a hemoglobin F level greater than 50%, responsive to hydroxyurea and splenectomy in the majority of patients. Genetic analysis was performed in half of the patients, which identified the *XMN1* gene mutation. Patients with minor thalassemia had a hemoglobin A2 level greater than 3.5%. All of the patients with thalassemia major and intermedia received calcium, folic acid, multivitamins, and zinc supplements. Iron-chelating agents were applied for major and intermedia variants. Splenectomy was performed in those requiring a transfusion volume greater than 250 mL/kg/y. A summary of patients' care plan for major and intermedia groups is shown in Table 1.

Blood pressure was measured by mercury monometer. Hypertension was defined as blood pressure greater than the 95 percentile for age, height, and sex in 3 separate occasions within 2 weeks. Fresh first morning urine and fasting blood samples were collected from each patient and were used for urinalysis and measurement of sodium, potassium, calcium, phosphorus, magnesium, uric acid, protein, creatinine, osmolality. Applied laboratory methods consisted of ion selective electrode for serum and urine electrolytes and colorimetry (Cobas, Rcohe) for urine and serum glucose, urea, creatinine (Jaffee method), uric acid (uricase method), calcium (thimol Blue method),

Table 1. Periodic Care of Patients With β-Thalassemia

Parameters	Thalassemia Major	Thalassemia Intermedia
Body weight	Every 3 months	Every 3 months
Height	Every 3 months	Every 3 months
Head circumference	Every 3 months	Every 3 months
Liver and spleen examination	Every 3 months	Every 3 months
Follicle-stimulating hormone, luteinizing hormone, estrogen, progesterone, androgen	Every 6 months	Every 12 months
Thyroid-stimulating hormone, T3,T4, T3 resin uptake	Every 6 months	Every 12 months
Parathyroid hormone	Every 6 months	Every 12 months
Alanine and aspartate aminotransferase	Every 6 months	Every 12 months
Blood urea nitorgen, serum creatinine	Every 6 months	Every 12 months
Viral infections tests	Every 6 months	Every 12 months
Abdominal ultrasonography	Every 12 months	Every 12 months
Cardiac and liver magnetic resosnance imaging	Every 12 months	Every 12 months
Echocardiography	Every 12 months	Every 12 months
Bone densitometry	Every 12 months	Every 12 months

and protein. Urine osmolality was assessed by an osmostat device. Tubular function was assessed by measuring sodium fraction excretion, transtubular K gradiant, magnesium fraction excretion, Calcium-creatinine ratio, uric acid-creatinine ratio, maximum tubular phosphorus reabsorption, and urine osmolality. Pyuria and hematuria were defined as leukocyte and erythrocyte counts of 5 per high-power field and more.

Viral infections, serum ferritin level, and urine albumin were tested by electrochemiluminescence assay (Elecsys Roche) in 2 groups of major and intermedia variants. Hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antigen and antibody test results less than 1 IU and a hepatitis B antibody test less than 10 IU were considered negative.

Glomerular filtration rate was calculated using the Schwartz formula (k × height/creatinine, where k = 0.55 in children older than 2 years old and 0.44 in those younger than 2 years old). Kidney dysfunction was defined as a GFR less than 90 mL/min/1.73 m^2 and glomerular hyperfiltration as a GFR greater than 120 mL/min/1.73 m^2.

Renal ultrasonography was performed in all patients by 1 radiologist for evaluating renal length, echogenicity, parenchymal thickness, and the presence of nephrolithiasis. Based on patients' age, normal renal lengths were 80 mm to 115 mm, 75 mm to 120 mm, and 67 mm to 118 mm for major, intermedia, and minor groups, respectively. In addition, bone densitometry was performed in 2 groups of major and intermedia variants at the time of analysis by a DXA machine/Fan beam (DEXXUM-T model, Osteosys).

The chi-square and the analysis of variance tests were used for the comparison of qualitative and quantitative variables, respectively. Analysis of meaningful variables was performed by the Tukey Post Hoc test. A *P* value less than .05 considered significant.

RESULTS

The study was conducted on 72 patients with β-thalassemia comprising 25 major, 23 intermedia, and 24 minor variants. The mean age at the time of study was significantly higher in the minor group, and it was significantly lower at first transfusion in the major (14.2 ± 13.5 years) than the intermedia type (56.0 ± 45.7 years; *P* = .001). The majority of the patients with major thalassemia were males, and females were more common in the intermedia and minor groups.

Blood pressure was normal in most of the patients. Renal ultrasonography showed normal-sized kidney, with normal echogenicity and renal parenchymal thickness in all of the patients, except for nephrolithiasis in 2 patients with thalassemia major and minor. Bone mineral density was significantly lower in the patients with thalassemia major. Demographic data of all patients are presented in Table 2.

Blood transfusion was done every 3 to 4 weeks in the major group, and only 1 intermedia patient experienced blood transfusion. Desferal was used in 20% of the patients in the major group and 8.7% of those with intermedia variants. Desferoxamine (including osveral and exjade) were used in 80.0% of the major group versus 69.6% of the intermedia. About 21% of the latter group did not need chelating treatment. None of the patients had hepatitis B, hepatitis C, or human immunodeficiency virus infection, except for hepatitis C infection in 1 patient with the major variant.

Estimated GFR was nonsignificantly higher in both the major and the intermedia groups compared to the minor variant. Serum level of all variables were within normal limits, with no significant

Table 2. Comparison of Demographic Characteristics of Patients With β-Thalassemia

Parameter	Major	Intermediate	Minor	*P*
Mean age, y	22.64 ± 6.49 (11 to 32)	20.91 ± 7.54 (9 to 37)	32.33 ± 10.33 (7 to 46)	< .001
Mean age at first transfusion, mo	14.16 ± 13.45	56.00 ± 45.66	…	.001
Sex, %				
Male	60.0	43.5	29.2	
Female	40.0	56.5	70.8	.57
Hypertension, %	4.0	4.3	18.8	.17
Hepatosplenomegaly, %	32.0	30.4	0	.91
Osteopenia, %	8.0	17.4	…	.02

difference among the three groups. However, serum calcium and phosphorus were lower in thalassemia minor, possibly due to lower health monitoring and no supplement intake. Based on mild hemolysis, serum ferritin level was significantly lower in the minor group, compared to the others (Table 3).

Urine level of all variables were normal in the majority of the patients, with a significantly lower urine phosphorus and uric acid excretion in the minor variant. Abnormal urinary variables are summarized in Table 4. Urine phosphorus and uric acid excretion increased more frequently in the major and intermedia groups, compared to the minor variant (Table 4). A small number of patients (4% to 8%) had hematuria and pyuria, with no significant difference between the types ($P = .79$, $P = .86$, respectively).

DISCUSSION

Both tubular and glomerular dysfunction might occur in children and adolescent with β-thalassemia secondary to decreased adenosine triphosphatase production, oxidative stress, lipid peroxidation, protaglandine imbalance, hyperdynamic cardiovascular system, increased renal blood flow, glomerular hyperfiltration, and late-onset afferent arteriole vasoconstriction.[9-12] Proximal tubular dysfunction has been reported in 13% to 60% of patients with β-thalassemia, especially in splenectomized major variant. It is characterized by increased urinary excretion of sodium (29%), calcium (13% to 32%), phosphorus (8%), magnesium (8%,) uric acid (38% to 52%), amino acids (30%), N-acetyl glucosamine (60%), β2-microglobuline (33% to 60%), retinol binding protein (69%), and glucose (7%) along with decreased urine osmolality.[2,13-15]

We showed no significant tubular dysfunction in our patients. Urinary excretion of all variables were normal in the majority of patients, especially in the minor group. About 8% to 13% of our patients had mild hypercalciuria along with increased urine sodium (13% to 24%), potassium (8% to 20%), and magnesium excretion (17% to 36%), which were not different between the three different variants. Urine phosphorus and uric acid increased in 8% to 48% and 13% to 56% of our patients, respectively, which were more common in major and intermedia variants. Patients with thalassemia minor had lower frequency of hyperuricosuria and phosphaturia in our study. About 20% of our patients had low urine osmolality, with no significant difference between the different groups.

Similar to our results, GFR and tubular excretion of sodium, uric acid, albumin, and β2-microglobulin

Table 3. Comparison of Serum Variables Between Patients With β-Thalassemia

Parameter (Reference Range)	Major	Intermediate	Minor	*P*
Hemoglobin, g/dL (12 to 15)	9.11 ± 0.94	9.26 ± 1.34	11.2 ± 1.14	.65
Fasting blood glucose, mg/dL (< 100)	93.48 ± 12.97	86.78 ± 11.67	90.87 ± 10.01	.14
Sodium, mg/dL (135 to 145)	138.3 ± 1.68	138.2 ± 1.21	137.7 ± 1.90	.80
Potassium, mg/dL (4.1 to 5.5)	4.40 ± 0.35	4.35 ± 0.31	4.27 ± 0.27	.39
Calcium, mg/dL (8.5 to 10.2)	9.34 ± 0.51	9.35 ± 0.42	8.92 ± 0.41	.005
Phosphorus, mg/dL (3.5 to 5.5)	4.66 ± 0.69	4.80 ± 0.89	3.68 ± 0.76	< .001
Magnesium, mg/dL (1.7 to 2.2)	1.98 ± 0.17	2.05 ± 0.24	1.88 ± 0.28	.08
Uric acid, mg/dL (2.5 to 7.5)	4.46 ± 1.42	5.78 ± 1.84	4.45 ± 1.43	.008
Ferritin, mg/dL (20 to 300)	1126.50 ± 880.07	827.09 ± 856.94	71.10 ± 74.58	< .001
Glomerular filtration rate, mL/min (90 to 120)	145.58 ± 22.17	153.89 ± 25.88	110.56 ± 24.13	.24

Table 4. Frequency of Abnormal Urinary Variables Between Patients With β-Thalassemia

Parameter (Reference Range)	Major	Intermediate	Minor	*P*
Protein-creatinine ratio, mg/mg (< 0.2)	4	4.3	4.2	> .99
Calcium-creatinine, mg/mg (< 0.2)	12	13	8.3	.86
Uric acid-creatinine, mg/mg (< 1)	24	56.5	13	.004
Sodium fraction excretion, % (≤ 1)	24	13	17	.55
Transtubular potassium gradient (5 to 15)	8	0	21	.55
Maximum tubular phosphorus reabsorption (2.3 to 4.3)	48	39	8	.008
Magnesium fraction excretion (≤ 5%)	36	17	25	.34
Urine osmolality (500 to 800)	20	21	21	.99

were well preserved in thalassemia minor as reported the previous studies.[16,17] In addition, significant renal involvement was an uncommon complication in children and young adults with major and intermedia variants,[5,18] and most of them presented with asymptomatic kidney dysfunction.[2]

Increased protein excretion is one of the most common manifestations of renal involvement in 70% of patients with thalassemia.[2] The most common cause of proteinuria are prostaglandine imbalance, prolonged hyperfiltration, and glomerular sclerosis.[8] Proteinuria had a positive correlation with serum ferritin, hemolysis, and iron overload, in addition to a negative correlation with hemoglobin level in Ziyadeh and coworkers' study.[19] About 4% of our patients had proteinuria and protein excretion was normal in the majority of all the three variants. However, it was significantly lower in thalassemia minor, which could be explained by the less severity of pathophysiologic mechanisms in this group of patients.

Glomerular filtration rate increases in young thalassemic patients, with irregular transfusions, increased dietary calcium intake, and lower iron storage.[19,20] However, progressive kidney dysfunction occurs in older age, prolonged and high intensity transfusion, increased urine calcium, phosphorus, and uric acid excretion, and high dose deferoxamine treatment.[12,21] Estimated GFR was nonsignificantly increased in both thalassemia major and intermedia in our study, which could be secondary to anemia and reduced systemic vascular resistance with further increase in renal plasma flow and glomerular filtration rate.[12] Similar to our results, GFR had no significant change in Lai et al study and was within normal range after following for 10 years.[12] In addition, GFR was preserved in all patients with major thalassemia in Ahmadzadeh and colleagues study.[15]

Serum ferritin has been suggested as a marker of renal tubular damage, which improves after chelating therapy.[9] Serum ferritin was significantly lower in our patients with thalassemia minor, which denotes to the lower frequency of tubular dysfunction in this group of patients. Microscopic hematuria has been reported in 7% to 10% of patients, more common in intermedia compared to the major variant.[1,5,15] The most common cause of hematuria was nephrolithiasis, secondary to increased urine calcium and uric acid excretion in Ali and coworkers' study.[5] The incidence of hematuria increases with older age, duration of blood transfusion, iron deposition, and desferoxamine treatment. Proteinuria and pyuria have been reported in 17% and 4% of patients, respectively, especially in association with hematuria.[1] Hematuria and pyuria occurred in 4% to 8% of our patients with no significant difference between the different variants.

CONCLUSIONS

To our knowledge, this is the first study comparing renal tubular and glomerular function in all three variants of β-thalassemia. A low number of patients in each group in addition to the lack of more specific tests for evaluation of tubular dysfunction were main limitations of this study. Our study showed that kidney function indicators were within the recommended range with no significant tubular and glomerular dysfunction in the three different variants of β-thalassemia.

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CONFLICT OF INTEREST

None declared.

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