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Comparative Evaluation of Glomerular and Tubular Function Abnormalities in Patients with Different Forms of β-Thalassemia, an Emerging Concern

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Abstract

Thalassemia syndromes are the most prevalent hereditary hemoglobinopathy in the world. Reduction or absence of β-chain synthesis is the hallmark of β-thalassemia syndromes, resulting in an excess of alpha chains. In all of the patients with thalassemia major (TM) and some patients with thalassemia intermedia (TI), repeated and regular transfusions are the main part of treatment. In β-thalassemia minor, the patients are asymptomatic and diagnosis is often based upon hematologic parameters on CBC and hemoglobin electrophoresis. Both tubular and glomerular dysfunctions have been reported in three forms of β-thalassemia, but these changes are more prominent in TM and TI. Iron overload due to repeated transfusions, chronic anemia, and the toxicity of iron chelator drugs such as deferoxamine and deferasirox are the main factors in the pathogenesis of nephropathy in patients with transfusion-dependent thalassemia (TDT). In this review, the mechanism of renal disease in thalassemia, comparative assessment of kidney dysfunction in three variant forms of β-thalassemia, and markers of tubular and glomerular dysfunction have been discussed.

Keywords: Thalassemia; Anemia; Kidney; child.

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Introduction

Thalassemia syndromes are the most prevalent single gene disorder worldwide. Reduction or absence of β chain synthesis is the most important hallmark of β thalassemia syndromes resulting in precipitation of α-chains in the erythroid precursor cells. The three classifications of β thalassemia are defined by their clinical and laboratory findings. In β- TM, there is a complete absence of β chain synthesis (β° / β°) while the production of β chain globin is reduced in patients with β-TI (β^+/β^+) (1).

Some β-TI patients remain asymptomatic throughout life, although some of them become symptomatic from early childhood. Indeed, the severity of β-TI correlates with the degree of imbalance between α and non-α chains as well as other genetic factors such as Xmn-1 polymorphism, which can modify the disease course (2). β-thalassemia minor is a heterozygous state that is usually asymptomatic with mild anemia. These patients carry one normal beta globin allele and one beta thalassemia allele on another chromosome. The peripheral blood smear in β thalassemia trait shows profound microcytosis and hypochromia. These patients do not need any treatments (3).

All patients with thalassemia major and some patients with β-TI need life-long transfusions and the consequence of these repeated transfusions is iron deposition in different vital organs. Therefore, these patients need iron chelator drugs (4). Some patients with β-TI especially those with homozygous Xmn-1 polymorphism do not need regular transfusions and can be treated with hydroxyurea and splenectomy (5, 6). Iran is located on the thalassemia belt (7). The thalassemia prevention program started in the country in 1997 (8). In recent decades, with advances in the transfusion protocols and chelation therapy, the

survival of thalassemia patients has improved dramatically.
Therefore, some unrecognized complications of this disease have been identified.
One of these morbidities is renal injury, which presents as glomerular and tubular dysfunction (9).

Mechanisms leading to renal abnormalities in thalassemia

Iron overload, chronic anemia, and toxicity of iron chelator drugs are the main mechanisms leading to renal injury in these patients. Other factors responsible for kidney disease in thalassemia include hepatitis B or C, HIV infection, iron-induced hepatitis, and chronic dysfunction (10).

Iron overload

Repeated regular transfusions can lead to hemosiderin deposition in proximal and distal tubules, cortical atrophy, interstitial fibrosis, and tubular necrosis (10). Moreover, free iron can facilitate lipid peroxidation and cell injury (11). Serum ferritin and liver hemosiderosis have a positive correlation with urine markers of tubular dysfunction (12). Ali BA and colleagues found that cystatin C had a strong positive correlation with serum ferritin in β thalassemia patients (13). Hashemieh et al. studied 120 transfusion dependent thalassemia patients and reported a moderate correlation between serum ferritin and kidney MRI T2* relaxation time (14). In a large study from Iran in 821 β-TM and β-TI patients, the authors found that 20% of patients had renal iron overload by means of MRI T2*. Moreover, they reported a moderate negative correlation between kidney MRI T2* relaxation time and serum ferritin (15).

Chronic anemia

Chronic anemia and hypoxia have an important role in oxidative stress and lipid peroxidation, which may result in tubular cell dysfunction. Chronic hypoxia in tubular cells may cause apoptosis and tubulointerstitial injury. This cell injury leads to glomerulosclerosis and kidney fibrosis (16). Furthermore, hyperfiltration and hyperdynamic circulation have been shown in thalassemia patients (17).

Toxicity of iron chelator drugs

All iron chelators (deferoxamine, deferiprone, and deferasirox) may lead to glomerular dysfunction (16). The kidney toxicity of deferoxamine and deferosirox are more than deferiprone, especially in the absence of dose monitoring. Moreover, iron depletion due to high doses of iron chelators has a key role in the pathogenesis of kidney disease (10).

Type of renal injury

Both types of kidney injury, i.e. tubular and glomerular dysfunction, have been reported in thalassemia patients (18).

Glomerular dysfunction

In thalassemia patients, anemia can reduce systemic vascular resistance, resulting in a hyperdynamic circulation and a subsequent increase in the renal plasma flow and GFR. Glomerular hypoperfusion and hyperfiltration can lead to stretching of the glomerular capillary wall. These changes may lead to epithelial and endothelial cell injury and a progressive decline in GFR over time (19). Moreover, tubular injury in childhood may result in abnormal estimated glomerular filtration rate (e-GFR) in adulthood (20).
Hamed and El-Melegy studied 69 children with β-TM and found significantly higher levels of cystatin C in these patients (21). Cystatin C is a marker of glomerular dysfunction and the use of this marker alone or in combination with creatinine improves risk assessment in end-stage renal disease (22).

Tubular injury

There are several reports of tubular damage in TDT population. Low molecular weight proteinuria is the most prevalent manifestation in these patients. Urinary markers of tubular damage such as N-acetyl β - D glucoseaminidase (NAG), β-2 microglobulin, calcium, phosphate, magnesium, uric acid, amino acid and malondialdehyde are increased in thalassemia patients (10).
Sadeghi–Bojd and colleagues studied 166 children with β-thalassemia major and reported hyperuricosuria (38%), proteinuria (8.6%), hypercalciuria (12.9%), phosphaturia (9.2%), and magnesiuria (8.6%) (23).
Mohkam and colleagues studied 103 children with β -TM and reported abnormal levels of urinary NAG, fractional excretion of sodium (FENa), potassium (FEK) and uric acid (FEUA) in 35.9%, 29.1%, 7.8%, and 52.4% of the patients, respectively (24). Increased urinary excretion of NAG has been reported in many studies (9, 11, 12,

25, 26). Hypercalciuria is found in many thalassemia patients (24, 25, 27, 28). More invasive transfusion protocols in TDT such as the super transfusion regimen correlate with increased frequency of hypercalciuria (27).

Early detection of kidney involvement in thalassemia major

Detection of renal disease in β-TM using traditional markers such as BUN and serum creatinine has remained unchanged for a few decades. However, novel biomarkers could be helpful in recognizing tubular and glomerular dysfunction in early stages (9).

Among these markers, serum cystatin C is a useful and sensitive marker for early recognition of glomerular injury. Other markers such as NAG, urinary β-2 microglobulin, urinary alpha-1 macroglobulin, neutrophil gelatinase associated lipocaline (NGAL), kidney injury molecule -1 (Kim-1) and urinary retinol binding protein (RBP) are recognized as novel biomarkers for early recognition of renal disease (9,10). Liver type fatty acid binding protein (L-FABP) is another marker that has been found to be effective in early diagnosis of acute kidney disease. Moreover, this marker can be used as a sensitive predictor of chronic kidney disease (29, 30). Some of these markers such as cystatin C (13, 25, 31-33), NAG (9, 11, 12, 24-26, 34, 35), and β-2 microglobulin (23, 25, 28, 32, 34, 36, 37) were studied in patients with major thalassemia in several published articles. Unlike these markers, few studies have investigated NGAL, Kim -1, RBP, and L-FABP. Sen and colleagues studied 52 patients with β-thalassemia major and found a significantly higher urinary NGAL to creatinine ratio compared to the control group (9). Furthermore, Roudkenar et al. conducted a study in 25 adults and 9 pediatric patients with β-TM and found upregulated NGAL expression only in adult patients compared to the normal group (38). Tantawy and colleagues conducted a study in 66 β-TM, 26 β-TI, and 40 healthy controls in Egypt and found that 69.4% of the patients have increased urinary levels of RBP (26). In another study, a significant positive correlation was found between ferritin and RBP (39). Furthermore, Sen and colleagues reported no difference in urinary Kim-1 to creatinine ratio between patients with β-TM and healthy controls in Turkey (9).

Kidney injury in thalassemia intermedia

Both tubular and glomerular dysfunction might occur in patients with thalassemia intermedia. Kidney injury is more prevalent in TM versus TI and it could start much earlier in TM compared to TI (40). Three main factors are held responsible for renal injury in patients with β-TI. Chronic anemia and hypoxia, iron overload due to ineffective erythropoiesis and exaggerated intestinal iron absorption, and finally intravascular combined extravascular hemolysis have an important role in the pathogenesis of kidney abnormalities in TI (41). The spectrum of kidney function disorders in patients with β-TI varies from subclinical mild abnormalities in the kidney function tests to end-stage chronic kidney disease. In a study of 120 patients with TI in a chronic care center in Hazmieh, Lebanon, six patients underwent chronic hemodialysis, of whom two had proteinuria; a kidney biopsy showed mesangial cell proliferation with focal or segmental glomerulosclerosis (42). There are limited data about kidney injury in patients with β-TI (43, 44). The mean GFR in patients with β-TI is higher than the normal population indicating glomerular hyperfiltration (40). With advancing age, these patients have a steeper decline in GFR compared to normal individuals (42). In a cross-sectional study of 50 cases with β-TI and 58 subjects with β-TM, the authors found that children with β-TM had higher BUN and creatinine levels probably due to increased iron overload in the renal system. In addition, the patients with β-TM had lower calcium and phosphate levels compared to TI patients due to liver or parathyroid involvement (44). Microscopic hematuria is also more common in TI compared to TM (44, 45). This finding might be due to hypercalciuria or hyperuricosuria (44). Furthermore, ageing, iron deposition, duration of blood transfusion and deferoxamine treatment correlate with an increased incidence of hematuria in patients with β-TI (45). The mean level of serum cystatin C in patients with TM and TI are the same. Alpha–1 macroglobulin (Alpha-1 M) and fractional excretion of sodium (FENa), which are markers of tubulopathy, are similar in TM and TI patients. Moreover, the urine protein/creatinine ratio is significantly higher in TM and TI population compared to normal subjects. Another reliable marker for detection of tubular dysfunction is the

urinary RBP level, which is higher in TM versus TI (39).

Kidney function abnormalities in thalassemia minor

The number of studies about tubular dysfunction in thalassemia minor is limited. Low grade hemolysis of microcytic red blood cells, tubular iron deposition and toxins derived from erythrocytes may lead to renal tubular injury in adult patients with beta thalassemia minor (46). In a study of 41 patients with β-thalassemia minor and 20 healthy controls, 14.6% of the patients had hypercalciuria, decreased tubular reabsorption of phosphorus (TRP) with hypophosphatemia, hypomagnesemia, hypouricemia and tubular proteinuria. Moreover, increased urinary secretion of uric acid and sodium has been shown in patients with thalassemia minor. Increased levels of FENa indicate tubular dysfunction. In addition, there is a negative correlation between sodium and uric acid urinary levels and hemoglobin level (47). The urinary zinc level, which is an indicator of oxidative stress, is higher in β-thalassemia minor, but there is not a significant difference between these patients and healthy normal population (48). In another study of 50 thalassemia minor patients and 50 healthy control subjects conducted in Iran, renal tubular dysfunction was shown. Proteinuria (32%), β2-microglobin excretion (36%), calciuria (4%), phosphaturia (4%) and uricosuria (20%) were reported in these patients. The study found that fractional excretion of uric acid and potassium, creatinine clearance and tubular phosphorus reabsorption were significantly different between thalassemia minor patients and healthy control subjects (49). Moreover, the mean level of serum cystatin C is higher in beta thalassemia minor patients compared to the normal population (39). Some authors believe that due to increased urinary excretion of calcium in thalassemia minor, the incidence of osteoporosis is higher in these patients (47, 48).

Discussion

Kidney injury is still an underestimated morbidity in transfusion-dependent thalassemia patients. Many published studies have been investigated glomerular and tubular dysfunction in thalassemia major and intermedia (12, 13, 20, 21, 24-26, 28, 32, 34, 35, 42, 43), but the number of studies about kidney function abnormalities in β-thalassemia minor is limited (47-49). Repeated transfusions, toxicity of iron chelators, accelerated iron turnover, reduced RBC survival, and tissue deposition of excess iron are the most important factors in the pathogenesis of kidney injury in β-thalassemia syndromes (43). The kidney function abnormalities in TM and TI are comparable, but these changes are more profound in TM compared to TI (40). Renal tubular dysfunction in thalassemia minor is controversial and there are many conflicting results about tubulopathy markers in β-thalassemia minor. Cetin and colleagues studied 41 β-thalassemia minor patients. For a better analysis, they divided the patients into two groups: patients with anemia (group I) and patients without anemia (group II). Furthermore, 20 sex and age matched healthy subjects were enrolled in this study as the control group. The anemic group had increased fractional excretion of sodium (FENa) and uric acid (FEUA), and also increased urinary zinc excretion compared to patients without anemia and control group. Moreover, 14.6% of the patients showed significant signs of renal tubulopathy, such as hypercalciuria, hypophosphatemia, hypomagnesemia, hypouricemia, and tubular proteinuria. The authors concluded that renal tubular function abnormalities were not uncommon in thalassemia minor patients (47). Sadeghi-Bojd and colleagues studied 50 β-thalassemia minor patients and reported similar results. The authors found some evidence in favor of tubular dysfunction in β-thalassemia minor such as proteinuria, calciuria, phosphaturia, uricosuria and β-2 microglobulin excretion. In addition, the results of fractional excretion of uric acid and potassium, creatinine clearance and tubular phosphorus reabsorption showed a significant difference between beta thalassemia minor patients and healthy control subjects (49). Kalman and colleagues studied 32 children with β-thalassemia minor and 18 healthy controls and found that markers of tubulopathy such as FENa, FEUA, FEMg, and NAG were not statically different between beta thalassemia minor patients and the control group. Moreover, the urinary zinc level, which is an indicator of the oxidative stress, was higher in beta thalassemia minor patients compared to healthy controls, but the difference between these two groups was not statistically significant (48). The reason for these discrepancies about the kidney tubular dysfunction in β-thalassemia minor patients

may be the difference in age range of the participants in these studies. Furthermore, Cetin and colleagues reported that renal tubular dysfunction in β-thalassemia minor might have some late sequelae such as kidney stone and reduced bone mass (47). Greep and colleagues reported that β-thalassemia minor was a risk factor for osteoporosis due to hypercalciuria in these patients, but Kalef-Ezra and colleagues did not report such a risk (50, 51). Alon and colleagues found that hypercalciuria was a risk factor for hematuria and urolithiasis (52). However, some published articles have shown hypercalciuria in β-thalassemia minor patients. Kalman et al. found no significant difference in hypercalciuria between β-thalassemia minor patients and healthy control subjects (48).

Conclusion

Tubular and glomerular function abnormalities have been shown in three forms of β-thalassemia; however, kidney function impairment is more evident in TM compared to TI and could start earlier. Hyperuricemia and microscopic hematuria are more common in TI versus TM. Therefore, close monitoring and periodic assessment of the tubular and glomerular function are mandatory in patients with TM and TI. Tubular dysfunction is not a rare complication in β-thalassemia minor, but further studies with large sample sizes are needed to document tubular function impairment in patients with β-thalassemia minor.

Conflict of Interest

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