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Review Article

Change in Attitude in Renal Function in Major Beta Thalassemia

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Abstract

Thalassemia is a multisystemic disease in the field of hemolysis and chronic anemia caused by the erythropoietic disorder. The severe effects of iron overload from continuous blood transfusion iron chelators side effects, and involvement of multiple organs in thalassemias such as heart failure, liver, and endocrine dysfunction can all affect kidney function. Although there has been much debate about changes in renal function in thalassemia for many years, the presence of hyperfiltration and ultimately, decreased renal function in almost all studies. It seems for the researchers to look beyond kidney function in a thalassemia perspective, because of secretory biomarkers of proximal tubular renal cells that are sensitive to pathologic agents, which may be a good indicator of the courses of treatment and prognosis of patients. Future studies will be sooner or later.

Keywords: Thalassemia, Renal complications, Iron overload.

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Introduction

Thalassemia is a type of chronic, microcytic, and inherited anemia that is associated with defects in hemoglobin synthesis and the reduction in the life span of red blood cells (1). Beta thalassemia is more common than alpha-thalassemia (2). Although the quality of life for patients with beta-thalassemia has improved in recent years, complications are still a great challenge in these patients (2, 3).

Cause of renal complications in thalassemia

For the first time, renal dysfunction has reported in patients with beta-thalassemia major (βTM) (4). Nowadays, renal complications have been seen at an earlier age and researchers have considered early detection as an important issue (5). Three mechanisms are involved in the pathomechanism of renal complications in patients with βTM: chronic anemia, iron overload, and specific iron chelators (6). Chronic anemia and hypoxia lead to impaired renal tubular function by oxidative stress and lipid peroxidation (6, 7). Red blood cell hemolysis due to hypoxia is also effective in this process (8). Chronic anemia reduces vessel resistance and increased renal plasma flow and GFR (7, 8). Increased GFR eventually leads to increased matrix volume and cellularity, and these events lead to the onset of sclerosis. For a long time, stretching of the glomerular capillary wall followed by endothelial and epithelial injury cause to decrease in GFR and progressive kidney damage (6, 7).

Iron overload is a side effect of blood transfusion in βTM that leads to multi-organ dysfunction in the heart, liver, kidney, and endocrine system (9). It seems that iron deposition in renal tubes is the main cause of tubular damage. Iron overload can induce lipid peroxidation and produce free radical oxygen in kidney tubular cells and leads to cell damage (10). Damaged tubular cells secrete growth factors and cytokines, leading to tubule-interstitial fibrosis and glomerular sclerosis. Excess iron as a result of repeated transfusions in the form of hemosiderin

falls into the nephrons and deposition of hemosiderin in the paroxysmal and distal tubes leads to tubular necrosis in these patients (6).

Iron chelator drugs are another mechanism involved in renal dysfunction in the context of βTM. Evidence points to glomerular and tubular nephrotoxicity followed by usage of some drug (11, 12). The possible mechanism may be due to mitochondrial dysfunction and uninterrupted production of adenosine and adenosine triphosphate (13). All causes have been shown in figure 1.

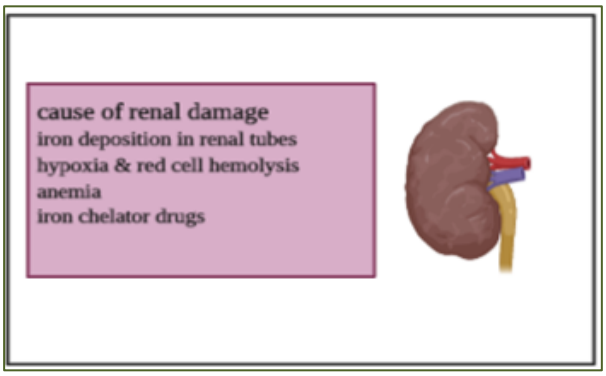

Figure 1. Cause of kidney damage in patients with major beta-thalassemia

Review of renal disease in thalassemia

The main focus of studies on kidney evaluation is on glomerular and tubular (proximal or distal) function. GFR is an important parameter for glomerular evaluation. Some studies have shown an increase in GFR whereas others have reported its decrease (14-16). In Lai ME et al. (8) study beta-thalassemia major patients had normal GFR during the ten years follow-up. This result has been in contrast to the study performed in Tabriz(16). They have found an elevation in GFR level (hyperfiltration) which indicates glomerular dysfunction. Since hyperfiltration has related to age, another study has evaluated a wider range of ages and the mean of GFR was higher (134 ± 35 mL/min/1.73 m^2 vs 154±66 mL/min/1.73 m^2) (15). Basma et al. (17) study on β-thalassemia major, also has shown that a significant percentage of patients have had glomerular dysfunction.

Usually, creatinine and albumin have used to evaluate tubular function. One study in Egypt has shown an increase in creatinine and a decrease in clearance of creatinine and GFR (17). In contrast, in some studies, creatinine, and clearance of creatinine have been in the normal range (15, 16, 18, 19). Since studies on creatinine and its clearance have shown different results, it is better to check early markers of renal dysfunction such as serum cystatin C, which is independent of age, sex, and muscle mass (20). The increase in cystatin C has been observed in previous studies that point to glomerular damage (14, 20). Alpha-1 microglobulin and retinol-binding protein (RBP) have been among new markers in examining the proximal tubular function and acute kidney injury (6). Tantawy et al. study has shown that 54.8% of patients with thalassemia have increased urinary excretion of alpha-1 microglobulin and 69.4% of them have increased urinary RBP levels. Alpha-1 microglobulin level has a positive correlation with serum ferritin and history of splenectomy in patients with thalassemia patients. RBP has had a negative correlation with creatinine and a positive correlation with ferritin and urinary total protein (21).

Proximal tubular damage has been associated with increases in low molecular weight protein in urine until tubular cell necrosis. It has been a common finding in thalassemia (22, 23). Almost all studies have been shown elevation in low molecular weight protein. The N-acetyl β-di glucose amine (NAG), β_2 microglobulin, calcium, phosphate, magnesium, and uric acid excretion also have been seen in a significant percentage of patients (22). In Sadeghi-Bojd et al. (9) study patients with βTM have had renal damage, such as hypercalciuria, proteinuria, glycosuria, magnesiumuria**.** They didn't measure GFR in their study that depends on factors like height, age, weight, race, and sex variables. Studies in sickle cell/beta-thalassemia (24) have shown an increase in cystatin C, NAG, and β_2 macroglobulin. Cystatin C and β_2 macroglobulin have a strong correlation with a clearance of creatinine and age. NAG has shown a correlation with proteinuria. Serum cystatin C and β_2 microglobulin level, proteinuria, and calciuria have been increased in Dimitriadou M et al. (14) study in βTM. The proteinuria has been also reported by the East Azerbaijan study (15). Harris et al. (25) reported

low blood pressure and proteinuria as a possible reason for the presence of interstitial renal tract disease. Prolonged hyperfiltration can cause proteinuria in patients with thalassemia. Ca/vitamin D consumption in most patients with thalassemia could lead to kidney stones and tubular damage (23). Tubulopathy with an increase in uric acid, phosphor, and urinary albumin, Ca, phosphor and uric acid have been reported in two studies (3, 9).

A study in 2015 has been shown new urinary markers in proximal tubular damage diagnosis such as NGAL (neutrophils gelatinase-associated lipocalin), KIM (kidney injury molecule), L-FABP (liver-type acid-binding protein). They have calculated the ratio of these parameters to creatinine in random urine, NGAL has shown an increase in beta-thalassemia compared with the normal group but there has been no correlation between urinary KIM and L-FABP to creatinine ratio between thalassemia patients and healthy controls (26).

Hypercalciuria, hyperuricosuria, hypophosphaturia, proteinuria, and changes in GFR have been some tubular and glomerular complications in major thalassemia.

Review of genetic factors in renal complications

Although there has been much debating about changes in renal function in thalassemia for many years, it's time to research the effects of genetic factors on the development of renal dysfunction in this group of patients (27). Researchers focus on Vitamin D receptor (VDR) polymorphism(shown in figure 2) because the kidney is one of the VDR target organs (28).

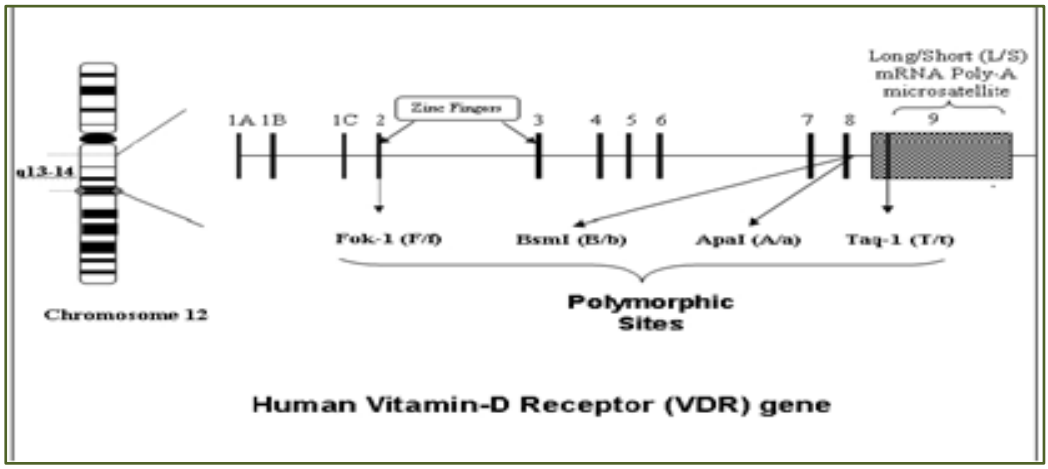

Figure 2. Vitamin D gene polymorphisms on chromosome

Dimitriadue et al. (14) have shown that patients homozygous for f allele (ff) in VDR, had increasing levels of cystatin C whereas, in Najafpour et al. (29) study, no significant correlation between renal dysfunction and FOK-I polymorphism have observed in VDR. Because studies about this matter as limited, more studies are needed to decide about the role of genetic factors in renal complications.

Review of drug complications

Iron chelator's side effects are important factors that show correlations with kidney disease. Pump dysfunction after treatment with deferoxamine (10), increased levels of creatinine and beta-microglobulin in deferazirox (30), glomerular and tubular dysfunction, and oxidative stress in deferoxamine (5) have been some of the drug side effects in thalassemia. A cohort study in patients under the treatment with deferazirox(with dosage: 20mg/kg/day) has shown tubular nephropathy with an increase in creatinine, β_2 macroglobulin, and magnesium, and decrease in GFR, potassium, calcium (12). A combination of deferazirox and silymarin (a herbal antioxidant), did not affect renal function, but the use of each drug lonely has been shown to decrease oxidative stress. They suggest that the co-interaction between two drugs, maybe the cause of this difference (31). Renal tubular dysfunction in patients with consumption of

deferazirox have suggested that it's better to check up renal function for prevention the renal involvement (32). Hypercalciuria during the consumption of deferasirox has been as another finding (15).

Conclusion

In conclusion, the renal complication is one of the major complications in patients with major beta-thalassemia. According to findings, we can detect early renal dysfunction with an evaluation of glomerular and tubular specific markers spatially genetic markers and prevent renal injury by monitoring the patients after the treatment with iron chelator drugs. So change of attitude to the role of genetic factors in renal failure in thalassemia can increase the quality of life in this group of patients.

Conflict of Interest

The authors declared that they have no conflict of interest.

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