Beta-thalassemia: renal complications and mechanisms: a narrative review

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ABSTRACT

Objective: Beta-thalassemias are a group of recessively autosomal inherited disorders of hemoglobin synthesis, which, due to mutations of the beta-globin gene, lead to various degrees of defective beta-chain production, an imbalance in alpha/beta-globin chain synthesis, ineffective erythropoiesis, and anemia. Improved survival in thalassemic patients has led to the emergence of previously unrecognized complications, such as renal disease.

Methods: A comprehensive literature review through PubMed was undertaken to summarize the published evidence on the epidemiology and pathophysiology of renal disease in thalassemia. Literature sources published in English since 1990 were searched, using the terms beta-thalassemia, renal disease.

Results: Renal disease is considered to be the 4th cause of morbidity among patients with transfusion dependent thalassemia. Chronic anemia, hypoxia and iron overload are the main mechanisms implicated in development of renal injury, whereas several studies also suggested a contributive role of iron chelators.

Discussion and Conclusion: Kidney disease may develop through progressive renal tubular and glomerular damage; thus, its early recognition is important in order to prevent and/or reverse deterioration. This review will provide an insight on the involved mechanisms implicated in kidney disease in thalassemic patients and will discuss the updates on diagnosis and prevention of renal complications in thalassemia.

Introduction

Beta-thalassemia syndromes are the most common inherited monogenic disorders worldwide. They are heterogeneous disorders caused by reduced or absent beta-globin synthesis, a major component of adult hemoglobin A (HbA, α2β2), leading to an imbalance of the globin chains [1]. Consequently, beta-thalassemia leads to reduced hemoglobin production and accumulation of α-globins which form insoluble hemichromes [2]. The former causes microcytic, hypochromic anemia; the latter is associated with oxidative stress, ineffective erythropoiesis and hemolytic anemia [3,4]. The clinical and hematological spectrum of beta-thalassemia disease ranges from mild to clinically overt conditions, including transfusion dependent (TDT) beta-thalassemia major (TM) and non-transfusion dependent (NTDT) beta-thalassemia intermedia (TI) or thalassemia minor (TMin) [5].

Thalassemia syndromes are prevalent in the Mediterranean, Africa and Southeast Asia [6]. Although they present a significant public health concern for the developing countries, population movements from countries where thalassemia is prevalent have also led to an increased number of affected patients in the developed countries [7]. At least 20.7% of the world population carry a beta-thalassemia variant, whereas annually approximately 40000 children are born with beta-thalassemia [8].

In recent years, mainly in developed countries, the prognosis of beta-thalassemia has improved due to blood transfusion, iron chelation therapy and the advances in the knowledge of the disease. In addition, the number of newborns with beta-thalassemia have been limited in Western societies due to the introduction of screening programs.

Despite the improved survival noted for beta-thalassemia, many patients experience complications in several systems, including cardiopulmonary disorders, endocrine organ diseases, liver impairment and thromboses in different vascular beds [9]. Furthermore, the improved patient survival has allowed previously unrecognized renal complications to emerge. The effect of thalassemia on the kidney has not been
extensively evaluated. The aim of this narrative review is to summarize information regarding the renal complications and their pathophysiologic mechanisms in beta-thalassemia patients. Literature sources published in English since 1990 were searched through PubMed, using the terms beta-thalassemia and renal disease or manifestations.

Epidemiology

Knowledge on the epidemiology of renal complications in beta-thalassemia is limited. Cross-sectional studies in various thalassemia groups from five thalassemia centers in North America have shown reduced creatinine clearance in 7.8%, and albuminuria in up to 59% of patients [10]. More recent studies, found renal dysfunction in 1.8% of TDT patients [11], whereas renal problems were classified as the fourth most common cause of morbidity (4%) after endocrine (44.7%), cardiovascular (41.3%) and hepatic (40.5%) disease in the same patient population [12].

However, there is currently no data from large observational cohorts on the prevalence of chronic kidney disease (CKD) following contemporary definitions in patients with beta-thalassemia.

Renal manifestations of beta-thalassemia

The study of renal function abnormalities in thalassemia is now timely, because of the increasing use of deferasirox and the patients’ improved survival. Several authors have reported abnormalities of renal tubular function in patients with thalassemia major and intermedia and others have suggested that renal hyperfiltration is common in patients with thalassemia.

The etiology, the pathogenetic mechanisms involved and the possible evaluation, including emerging biomarkers are presented in Table 1. The most common pathophysiologic and clinical manifestations of renal disease in beta-thalassemia patients are:

Tubular dysfunction

Evidence of tubular dysfunction among patients with beta-thalassemia was initially described about 2 decades ago by Ong-ajjooth et al [13]. Since then, several studies confirmed and evaluated further the

### Table 1. Renal disease in beta-thalassemia.

| Renal manifestation | Etiology | Mechanism | Evaluation/Biomarkers |
|---------------------|----------|-----------|-----------------------|
| Hematuria           | Nephrolithiasis | Hypercalciuria, hyperuricosuria, cystinuria, struvite stones | Dipstick urinalysis |
| Tubular dysfunction | Chronic anemia/hypoxia | Oxidative stress, lipid peroxidation, endothelial damage and loss of peritubular capillaries | Serum β2-M |
|                     | Iron overload | Oxidative stress, lipid peroxidation | Urine calcium/creatinine |
|                     | Aminoglycoside, intravenous radiocontrast agents, NSAIDs | Nephrotoxicity | Urine β2-M/creatinine |
|                     | Beta-lactames | Cytotoxicity, renal vasoconstriction, acute tubular necrosis. | Urinary NAGL |
|                     | Ampicillin, ciprofloxacin, sulfonamides, acyclovir | Mitochondrial dysfunction, lipid peroxidation, acute tubular necrosis | Urinary α1-microglobulin |
|                     | Urine dipstick | Crystal precipitation within the distal tubular lumen | Urinary RBP |
| Glomerular dysfunction | Chronic anemia/hypoxia | Reduced vascular resistance, elevated RPF | Serum creatinine |
|                     | Iron overload | Damage and loss of peritubular capillaries, epithelial-mesenchymal transdifferentiation of tubular cells to myofibroblasts, tubulointerstitial injury, glomerulosclerosis | Urine protein/creatinine |
|                     | Infections (e.g. HIV, HCV, HBV) | Glomerulonephritis | Serum cystatin |
|                     | Iron chelators | Relative iron depletion, mitochondrial dysfunction in tubular cells, tubuloglomerular feedback, vasoconstriction of the afferent arteriole | CrCl eGFR |
|                     | NSAIDs, COX-2 inhibitors | Glomerulosclerosis | 24-hour urine collection |
|                     | ACE inhibitors, ARBs | Vasoconstriction of the afferent arteriole | Radiographic studies |
| Nephrolithiasis     | Vitamin D, calcium supplementation, deferasirox, tubular dysfunction | Hypercalciuria, calcium stones | Urine dipstick |
|                     | Tubular dysfunction | Hypertension, cystine stones | Serum electrolytes |
|                     | Splenectomy increased red cell turnover, tubular dysfunction | Cystinuria, cystine stones | Serum creatinine |
|                     | Urinary tract infections by urease-producing bacteria (e.g. Proteus spp, Klebsiella spp, S.epidermidis, Mycoplasma spp, yeast species) | Hyperuricosuria, uric acid stones | 24-hour urine collection |
|                     | Struvite stones | Struvite stones | Radiographic studies |

Note: β2M: β2 microglobulin; NAG: N-Acetyl-beta-D-glucosaminidase; NAGL: neutrophil gelatinase-associated lipocalin; RBP: Retinol binding protein; RPF: Renal plasma flow; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NSAIDs: Nonsteroidal anti-inflammatory drugs; COX2: Cyclooxygenase-2; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin receptor blockers; CrCl: Creatinine clearance; eGFR: estimated glomerular filtration rate.
Table 2. Studies indicated or no tubular dysfunction in patients with beta-thalassemia.

| Authors            | Study type         | Number of patients | Age (years) | Chelation therapy | Biomarkers                           | Results-conclusions                                                                 |
|--------------------|--------------------|--------------------|-------------|-------------------|--------------------------------------|--------------------------------------------------------------------------------------|
| Koliakos et al, 2003 | observational      | 91 TM with no evidence of renal disease | 17.2 ± 7.2  | DFO               | Urine NAG, Urine IgG                 | - high incidence of renal proximal tubular dysfunction.                              |
| Papassotiriou et al, 2010 | observational   | 150 TM with no evidence of renal disease | 29.2 (6.4–44.2) | DFX               | Plasma NGAL, Cys C                   | Cys C concentration may be influenced by hemodynamic parameters as a result of therapy with DFX. |
| Ahmadzadeh et al, 2011 | case-control study | 140 TM with no evidence of renal disease | 7–16        | DFO               | Urine NAG, blood sample for biochemical and ferritin tests | Any changes in cys C do not reflect renal impairment. - Kidney dysfunction in thalassemia increases with increasing age, duration, and levels of bloodtransfusion and hypercalciuria. - The presence of severe renal dysfunction in thalassemic patients should be investigated using sensitive and specific tests, mainly NAG, to prevent progression. |
| Mohkam et al, 2008 | cross-sectional    | 103 TM with no evidence of renal disease | 12.5+/-5.53 | DFO               | Urine sodium (Na), potassium (K), calcium (Ca), creatinine (Cr), phosphate, uric acid (UA), NAG and amino acids | Urinary NAG excretion can be a reliable index of the tubular toxicity and a possible predictor of proteinuria, aminoaciduria and eventual renal impairment in these patients. |
| Michelakakis et al, 1997 | case-control study | 36 TM with no evidence of renal disease | 5–22        | DFO               | Urine specimens, Urine NAG, a-Mannosidase, ferritin | Iron overload resulted in increased urinary levels of the lysosomal enzyme NAG. Reduction of iron load, achieved by regular DFO infusion, resulted in normalization of the urinary enzyme levels. |
| Smolkin et al, 2008 | case-control study | 37 TM and 11 TI | 2.4–27    | DFO               | Urine and blood samples, Urine NAG | Renal tubular function is impaired in children with TM and TI. It is not known whether these functional abnormalities would have any long-term effects on the patients. |
| Tantawy et al, 2014 | cross-sectional    | 66 TM and 26 TI | 2.5–16    | DFP               | Serum ferritin, bicarbonate, plasma osmolality and urinary total proteins, microalbuminuria, NAG, RBP, α-1 microglobulin, bicarbonate, osmolality, creatinine clearance (CrCl) | Asymptomatic renal dysfunctions are prevalent in young β-TM and β-TI patients that necessitate regular screening. |
| Ong-ajyooth et al, 1998 | case-control study | 95 beta-thal/Hb E | na         | na                | Urine NAG, β2M Plasma and urine MDA | This is the first report of renal tubular defects found associated with beta-thal/Hb E disease. The mechanism leading to the damage is not known but it might be related to increased oxidative stress secondary to tissue deposition of iron, as indicated by the raised levels of serum and urine MDA. The increased NGAL levels reported for the first time in TI patients in agreement with the elevated expression of NGAL observed in T mouse models. The induction of NGAL may represent either a survival response, facilitating the survival of the less damaged thalassemic erythroid precursors, or a consequence of the abnormal iron regulation in Ti. |
| Patsaoura et al, 2014 | case-control study | 35 TI | 8–63        | -                  | Plasma NGAL, STR, NTBI, | The increased NGAL levels reported for the first time in TI patients in agreement with the elevated expression of NGAL observed in T mouse models. The induction of NGAL may represent either a survival response, facilitating the survival of the less damaged thalassemic erythroid precursors, or a consequence of the abnormal iron regulation in Ti. |
| Roudkener et al, 2008 | case-control study | 25 adults TM and 9 pediatric TM | 24.33 ± 7.09 and 8.28 ± 1.49 | na | Plasma NGAL with PCR and ELISA | - In all adult cases, except one sample, NGAL protein was expressed more compared to the controls - Positive correlation with ferritin - Negative correlation with sex, age - NGAL upregulation was not found in pediatric beta-thalassemia patients. Iron overload and oxidative stress in beta-thalassemia patients induce NGAL/Lcn2 expression. Upregulation of NGAL in this disorder may play a beneficial role in decreasing ROS or chelating iron. Obviously, chelating of iron is one of the major therapeutic goals in b-thalassemia. |

Note: TM: Thalassemia major; TI: Thalassemia intermedia; TMin: Thalassemia minor; DFO: Desferrioxamine; DFX: Deferasirox; NAG: N-Acetyl-beta-D-glucosaminidase; β2M: β2 microglobulin; NAGL: Neutrophil gelatinase-associated lipocalin; IgG: Immunoglobulin G; Cys C: Cystatin C; NT-proBNP: N-terminal pro b-type natriuretic peptide; RBP: Retinol binding protein; MDA: malondialdehyde; STR: Soluble Transferrin Receptor; NTBI: Non-transferrin-bound serum iron; hs-CRP: high-sensitivity C-reactive protein; PCR: Polymerase chain reaction; ELISA: Enzyme-linked Immunosorbent Assay; Lcn-2: Lipocalin-2; ROS: Reactive oxygen species.
tubular function in beta-thalassemia (Table 2). Up to 60% of patients with TDT have been reported to develop signs of tubular dysfunction [14]. Common signs of tubulopathy, such as proteinuria (8.6%), hypercalciuria (12.9%), phosphaturia (9.2%), hyperuricosuria (38%), magnesiumuria (8.6%), and increased excretion of β2-microglobulin (B2M) (13.5%) were demonstrated in a TDT Iranian population [15].

Early recognition of renal dysfunction is of great importance in terms of intervening in a timely manner and improving prognosis. Therefore, in the recent years, several molecules produced and released by proximal tubular cells as measurable proteins, have been tested as possible valid biomarkers of renal injury. Such proteins include N-Acetyl-beta-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), Liver-type Fatty Acid-Binding Protein (L-FABP) and Interleukin-8 (IL-8), all of which were studied mainly in children and younger patients with TM [16–18]. However, further research is needed to evaluate the significance of these biomarkers as predictors of renal disease in thalassemia patients.

Tubular dysfunction among patients with beta-thalassemia has been related to iron overload, chronic anemia, as well as desferioxamine (DFO) toxicity [19–22]. The mechanism of iron overload-associated renal damage has not been fully elucidated. Non-transferrin iron can lead to organelle membrane dysfunction and subsequent cell injury/death. Iron-catalyzed generation of reactive oxygen species (ROS) is responsible for initiating the peroxidative reaction. The possible association of oxidative stress and its impact on nitric oxide (NO) metabolism in iron overload associated renal injury was investigated through a randomized study on rats. In this study, animals were assigned into Fe-loaded (given 500 mg elemental iron/kg body weight as iron dextran; IV), Fe-depleted (given an iron-free diet for 20 weeks), and control groups. Chronic iron deposition in proximal tubules, glomeruli and interstitial matrix metabolism of renal cells and leads to the obliteration of peritubular capillaries [29–31], hypertransfusion program and DFO treatment, and moderate anemia (Hct > 25%). Patients with severe anemia had significantly higher low-molecular weight proteinuria and malondialdehyde (MDA, an indicator of lipid peroxidation), and lower urine osmolarity than those with moderate anemia. The abnormalities were the least severe in patients on hypertransfusion and DFO therapy [22].

Furthermore, splenectomy was proved to be an independent risk factor for tubular abnormalities. A cross-sectional, case–control study reported data among 40 splenectomized and 26 non-splenectomized patients with TM, aged 2.5–13 (mean 6 years). Increased levels of NAG (32 ± 14.3 U/g creatinine, p < .01 vs. 18.3 ± 15.2 U/g creatinine, p < .01), α-1 microglobulin (27.5 ± 13.6 mg/g creatinine, p < .01 vs. 13 ± 8.5 mg/g creatinine, p < .01) and also marked increase in serum ferritin (683 ± 160 ng/ml, p < .01 vs. 483 ± 227 ng/ml, p < .01) were found more frequently in splenectomized than in non-splenectomized patients [32].
Interestingly, improved renal function was illustrated in patients with TDT after curative hematopoietic stem-cell transplantation (HSCT). When comparing 29 children with TM who had undergone HSCT to 39 children of the same age and similar disease severity but who had not experienced HSCT, parameters of tubule function were better in patients that had undergone HSCT, as demonstrated by urine protein level (0.36 mg/mg creatinine vs 3.03 mg/mg creatinine, \( p < .001 \)), osmolality (712 mosmol/kg vs 573 mosmol/kg, \( p = .006 \)), NAG (17.7 U/g creatinine vs 42.9 U/g creatinine, \( p = .045 \)), and \( \beta 2 \)M (0.09 microg/mg creatinine vs 0.13 microg/mg creatinine, \( p = .029 \)) [33].

**Glomerular dysfunction**

Changes in glomerular function are also evident in multitransfused patients with beta-thalassemia. Chronic anemia is thought to reduce systemic vascular resistance leading to hyperdynamic circulation and subsequent increased renal plasma flow and glomerular filtration rate (GFR) [34]. Glomerular hyperfiltration appears to be deleterious to the mesangial compartment, causing it to increase matrix volume and cellularity, initiating a sclerotic process [35,36]. In the long-term, such modifications may theoretically lead to a progressive decline in GFR through the typical pathway of hyperfiltration – albuminuria – progressive renal damage. Furthermore, renal tubular cells that are subject to iron overload, induce injury into the interstitium by releasing cytokines and growth factors that may cause tubulointerstitial scarring and glomerular sclerosis [37].

As it has already mentioned, when iron exceeds the binding capacity of transferrin, as it occurs in iron overload, it accumulates as a non-transferrin-bound iron which accelerates the generation of radical oxygen species and cellular damage.

Additional contributing independent factors to renal injury may be glomerulonephritis induced by HIV, hepatitis B and hepatitis C infections, as well as non-iron related liver and heart disease [38].

In studies performed in children, adolescents [10,39] and adults with TDT receiving iron chelation therapy [40], calculation of GFR based on serum creatinine concentration or creatinine clearance demonstrated glomerular hyperfiltration. It is worth mentioning that Milo et al demonstrated reduced GFR in 9 TDT patients through the use of inulin clearance [41]. Individuals were on chelation therapy with DFX for at least 1 year. All patients had lower inulin clearance and GFR than normal healthy young adults, while 4 out of 9 patients had mild to moderate chronic kidney disease (CKD). By using Cockcroft-Gault (CG) equation and serum creatinine, median creatinine clearance in the same study was 134.9 (mean 133.3) mL/min per 1.73 m², significantly higher than the GFR estimated by inulin clearance (\( p < .008 \)) [41].

Economou et al, who used cystatin C (Cys C) in 42 pediatric and adult patients with TM, also described a reduction in GFR compared to normal controls (\( p \leq .001 \)). On the contrary, compared to normal levels, elevated Cys C levels, were also significantly accompanied by other indexes of glomerular dysfunction, such as proteinuria (223.28 ± 125.84 and 79.34 ± 29.1 mg/m²/day, respectively, \( p < .0001 \)). All patients of the study were chronically transfused and under a regular chelation program, which consisted of either DFX or combination of DFP and DFO [42]. Similarly, elevated Cys C levels were also visualized in TM patients not receiving chelation therapy [43]. Another study found a very weak inverse linear correlation between serum ferritin and Cys C eGFR, which, however, was not observed when concomitant use of chelation therapy was considered [44]. Prospective and larger studies are needed to validate these findings.

Quinn et al applied 24-h urine collection and reported similar levels of creatinine clearance (mean 136.1 mL/min per 1.73 m²) in 106 adult patients with TM, the majority of whom were treated with DFP or DFO. When they assessed GFR using this method, they predicted hyperfiltration [10]. On the other hand, Piga et al reported normal GFR measured by plasma sampling of 51Cr EDTA in patients with TM [45].

Taking everything into consideration, the estimations regarding GFR are frequently varying and inconsistent. Most of the times these variations apparently derive from the different parameters applied in each study. Patient demographics, clinical characteristics, comorbidities and iron chelation therapy, in addition to the study design and data analysis, are important factors that might influence the outcome of each study.

Milo et colleagues propose inulin clearance as a more accurate method to the early detection of reduced GFR and deceleration of the progressive deterioration toward CKD. According to the authors, it is important to note that the same study has some limitations such as the fact that it involves a relatively small number of participants. Additionally, it is a cross-sectional study and all participants were adults (median age was 30, range 21–37 years) [41].

Reduced estimated GFR based on serum creatinine (MDRD study simplified equation), has also been demonstrated in a cohort of TM adult patients regularly followed-up for 10 years [46]. As in the previous study, all patients were transfusion-dependent, treated with iron chelation, and they were adults at the time of the enrollment. Thus, it is unclear whether hyperfiltration preceded the demonstrated reduced GFR or it never existed. This theory could be supported by similar studies conducted on children with TM, but to
our knowledge there is no current reference presenting such data.

Other factors that favor glomerular hyperfiltration are the male gender and history of splenectomy, according to data derived from univariate and multivariate analysis among adult, multitransfused patients with TM and TI [47].

The variability of GFR estimations might, indeed, be related to the method used for GFR calculation. Equations based on serum creatinine (e.g. CKD-EPI, MDRD) overestimate GFR due to the low serum creatinine levels observed in patients with TM, which might be related to their muscular atrophy and reduced muscle mass [48,49], and, therefore, decreased generation. On the contrary, urinary creatinine excretion in healthy people is expected to equal creatinine generation [50], most of which is generated by muscle metabolism [50]. Other possible factors contributing to low serum creatinine in thalassemia patients are compensated by increased tubular creatinine secretion which prevents its appropriate rise in serum [51], or extrarenal creatinine metabolism, especially when kidney function is reduced [52]. Lastly, variability in serum creatine measurements among individuals may additionally contribute to overestimation of GFR [50].

Calculation of GFR based on creatinine clearance (e.g. Cockcroft-Gault Equation) might also result in overestimation of GFR, which may be encountered as hyperfiltration. In this case, increased creatinine clearance is, largely, due to the proximal tubular secretion of creatinine. Urinary creatinine excretion consists of filtered creatinine and proximal tubular secretion of creatinine. As glomerular disease progresses, the remnant tubular cells hyper secrete creatinine, resulting in increased creatinine excretion and, thus, elevated creatinine clearance [51].

Measurement of the area under the plasma clearance curve (AUC) following a single intravenous injection of 51Cr-EDTA, is another procedure for determining GFR. Similarly, to the aforementioned methods, it has been proven that measurement of GFR by 51Cr-EDTA overestimates the true renal clearance by approximately 10% [53].

Cys C is a low molecular weight proteinase inhibitor that is produced in all nucleated cells and maintains a constant appearance rate in blood. Opposed to serum creatinine, serum Cys C concentration is independent of gender and muscle mass [54]. Cys C is freely filtered through renal glomeruli and then totally reabsorbed and catabolized in the proximal renal tubule and does not return to the blood. Therefore, serum concentration is mainly determined by GFR [55]. Previous studies have demonstrated the superiority of serum Cys C compared to Cr in the evaluation of GFR, especially when there is a minor reduction in GFR [56,57].

Inulin clearance is the most widely accepted method for estimating GFR [58]. However, this is a method that, due to its complexity, cannot be consistently used in clinical practice.

Considering the above it is rather obvious that the use of an accurate method to evaluate the GFR method may lead to early detection of reduced GFR and delay the progressive deterioration toward chronic kidney disease.

Hematuria

An Iranian study involving a comparative evaluation of 108 children with beta-thalassemia TDT or NTDT demonstrated microscopic hematuria in 19 patients. Interestingly, hematuria was more common in NTDT than TDT (90% vs. 10%) [59]. A subsequent study, revealed the presence of microscopic hematuria in 10.6% from a total of 500 patients with TDT, while, at the same time, its frequency was significantly increased in ages over 20 years (9.8% vs. 20%, p = .04) [60]. The presence of hematuria might be related to either hypercalciuria or hyperuricosuria and nephrolithiasis [59].

Nephrolithiasis

The prevalence of nephrolithiasis in TDT population might reach 59%, as demonstrated in a study involving 27 subjects with TM by non-iodinated contrast renal tract CT. Among the affected subjects, 69% had multiple stones, whereas 56% of the affected patients had stones of variable composition. The majority of renal calculi were struvite (33%), followed by calcium oxalate (31%) and cystine (22%). The development of struvite stones may warrant an evaluation of an underlying infection [61].

Through a retrospective study of 166 participants with TDT, Wong et al showed that nephrolithiasis is associated with reduced bone mineral density of the femoral neck (odds ratio (OR) = 5.59, 95% CI 1.16–27.03) and increased risk of fracture in males (OR = 2.13) [62].

It is worth mentioning that stone formers in this study had elevated creatinine and lower ferritin serum levels suggesting that DFX is involved as a causative factor [62]. The impact of hypercalciuria after vitamin D and calcium supplementation on renal stone development in the general population remains controversial [63,64]. Similarly, calcium or vitamin D supplementation was not found to be a risk factor for kidney stones in individuals with thalassemia [61]. As we already know, hyperuricosuria due to tubular dysfunction and increased cell turnover has been associated with uric acid urolithiasis in the general population. However, in TDT patients, uric acid stones represented only 2% of all stones, which
might be reflected by the increased frequency of blood transfusion, which limits cell turnover [61]. Splenectomy was proved to be an independent risk factor for the development of hyperuricemia and nephrolithiasis in patients with TI, by further increasing erythrocyte turnover and number. Despite xanthine oxidase inhibition, patients receiving allopurinol had both significantly higher level of serum urate and higher prevalence of urolithiasis, compared to those not receiving it (p < .01) [65].

The role of iron chelating agents in renal disease

The advent of iron chelators improved patient survival in beta-thalassemia. However, this achievement has allowed previously unrecognized complications to emerge.

Currently, three iron chelators are available: oral agents deferasirox (DFX), deferiprone (DFP), as well as parenteral deferoxamine mesylate (DFO). Renal manifestations attributed to chelating agents are rare. Although serum ferritin levels have been inversely correlated with GFR [66], iron chelation therapy has also been related to renal function deterioration [67]. Oral agent DFP lacks support of large randomized controlled trials. About two decades ago, Hoffbrand et al studied the efficacy and safety of DFP in 51 transfusion dependent iron overloaded patients.

They reported that only 1 patient discontinued the drug after 4 months of treatment because of renal failure. However, that patient was not thalassemic [68]. El Alfy et al demonstrated a modest non-significant and non-progressive elevation in serum creatinine from a baseline mean of 29.2 ± 12–37.1 ± 10 micromol/L over a 6-month period, in a study of 100 children under 10 years old (mean 5.1 years) with TDT (91 patients with TM), to whom were prescribed 50–100 mg/kg DFP. Two patients had baseline serum creatinine values of 71 and 62 micromol/L, which resolved by the end of the study, while two others had a single but transient episode of elevation of serum creatinine above the upper limit of normal, which also resolved by the end of the study, without a need for interruption of therapy or dose adjustment [69]. The etiology for these fluctuations is unclear but has not been reported in other currently available data. Moreover, a case report has been published by Bragadesh et al. suggesting that the DFP may be an alternative iron chelator when renal impairment is obvious [70]. Although DFP is not considered nephrotoxic, it is characterized by a narrow therapeutic window and serious adverse effects, such as agranulocytosis, neutropenia and disabling arthropathy [71]. Thus, it is approved specifically for patients with TDT, when treatment with other chelating agents is contraindicated or inadequate.

DFX is well absorbed by the gastrointestinal tract, forms a complex with the plasma iron and is excreted via the hepatobiliary route. It also binds intracellular iron inducing ferritin degradation through proteasome mediated mechanism [72]. DFX is generally well tolerated. However due to its lipophilicity, DFX enters the tubular cells and forms a highly charged complex with iron. This triple negative charged DFX-iron complex does not penetrate membranes easily but accumulates and may result in proximal tubulopathy and Fanconi syndrome (FS) [73]. FS is associated with non-anion gap metabolic acidosis, hypophosphatemia due to phosphaturia, aminoaciduria, proteinuria and glucosuria (with normal serum glucose concentrations). Despite its importance, there is limited data about the risk factors, incidence and clinical picture of FS in patients receiving DFX. A retrospective study conducted by Chuang et al indicated a younger age of treatment initiation as the sole factor that was significantly associated with FS (7.8 vs. 19.2 years, p = .008) [74].

Similarly to other reports [75–83], patients in this study were not documented to have complete FS. FS generally affects less than 1% of patients, mainly those treated for more than 6 months [74–86]. Successful management is usual upon discontinuation of DFX and repletion of fluid and electrolyte deficits [75–77,81–83,86,87], while efficacy of plasmapheresis has not been confirmed [88]. Unfortunately, recurrence even after initiation of lower doses of drug may occur [77,82] (Table 3). Moreover, DFX at therapeutic doses in TM patients was also associated with hypercalcemia providing a biological mechanism for both increased kidney stones and accelerated bone resorption [89–91]. Dose-dependent increase in serum creatinine was observed in 38% of TDT patients treated with 20–30 mg/kg DFX.

However, this increase was sometimes transient, never exceeded two times the upper limit of normal (ULN) and was generally within the normal range [85]. Later studies on adult and pediatric patients with TDT and normal renal function, confirmed absence of progressive increase in serum creatinine over a 5-year follow up after treatment. An increase over 33% above the value at the start of DFX and greater than the ULN was reported in consecutive serum creatinine level, in 8.8% of the patients, mostly in doses 25–35 mg/kg/day. Nonetheless, this increase was manageable and did not lead to drug interruption [86]. On the other hand, a retrospective study of 72 patients (mean age: 20.3 ± 0.9 yrs; 36 male, 36 female) with thalassemia major or intermedia treated at Sultan Qaboos University Hospital found that the renal side effects related to deferasirox appear to be higher than those reported in published clinical trials [92]. Reassuringly, DFX proved to be safe in managing iron overload in
### Table 3. Deferasirox induced Fanconi syndrome.

| Authors                  | Study design                           | Patient population | Comorbidities/other potentially nephrotoxic medications | Dose and duration of treatment | Clinical picture                                                                                      | Outcome                                                                                      |
|--------------------------|----------------------------------------|--------------------|----------------------------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Chuang et al, 2015 [73]  | Cohort study, single center, evaluating the incidence of DFX-related FS and its risk factors. | 57 patients with TDT, aged 7.8 ± 4.4 years old | None | 9299 ± 1774 mg/kg/year for 6.9 ± 1.8 years | Non-anion gap metabolic acidosis, hypophosphatemia, glucosuria | DFX was stopped. All features of proximal tubular dysfunction resolved. |
| Rafat et al, 2009 [81]   | Case report                            | 78-year-old male with sideroblastic anemia | DM, CLL, aortic valve replacement, and essential hypertension/ perindopril, glibenclamide, metformin | 24 mg/kg/d for 1 month | Non-anion gap metabolic acidosis, hypophosphatemia, glucosuria, proteinuria, hypourichemia, increased β2-microglobulin urinary level. Increase in serum creatinine from 0.9–2 mg/dl | DFX was stopped. Resolution of tubulopathy apart from minimal proteinuria. Serum creatinine 1.2 mg/dl |
| Murphy et al, 2013 [79] | Case report                            | 21-year-old male with Ewing sarcoma | Ifosfamide | 1125 mg/d for 9 months | Hypophosphatemia, hypokalemia, glucosuria, proteinuria, kaliuresis. Increase in serum creatinine from 1.1–2.5 mg/dl. Kidney biopsy revealed severe tubular injury with tubular epithelial cells demonstrating isometric vacuolization consistent with drug toxicity | DFX was stopped. Fluid and electrolyte supplementation. |
| Shah et al, 2017 [89]   | Case report                            | 20-year-old male with TDT admitted for a scheduled allogenic stem cell transplant | Fludarabine | 20–30 mg/kg/d for 8 years. Due to dispensing error he received a one-time dose of 90 mg/kg. | Acute onset, following high dose administration. | Metabolic acidosis, glucosuria, hypophosphatemia, kaliuresis and elevated β2-microglobulinuria | DFX was stopped. Fluid and electrolyte supplementation. Plasmapheresis. All features of proximal tubular dysfunction resolved. |
| Papneja et al, 2016 [87] | Two Case reports, two centers          | 16-year-old male with DBA | None | 30 mg/kg/d for 6 years with a transient increase to a maximum of 45 mg/kg/day during the last year. | Non-anion gap metabolic acidosis hypokalemia, hypophosphatemia, phosphaturia, glucosuria, and proteinuria | DFX was stopped. Fluid and electrolyte supplementation. FS was resolved. DFX was restarted. |
| Dee et al, 2014 [75]    | Cohort study, single center, evaluating the incidence of DFX-related FS. | 9 patients with TDT, aged 2.6–23.8 years old | One patient had influenza virus H1N2 and developed severe hypokalemia while on DFX. Another patient had Echovirus type 6 infection 10 months before the onset of renal tubular dysfunction due to oxymethalone. | Dose was not indicated. Cumulative incidence was estimated at 11% at 2 months and about 90% at 6 years of DFX therapy | Metabolic acidosis (33%), elevated urine β2M (Odds ratio (OR) = 35.29, P = 0.0009), hypokalemia (OR = 23.22, P = 0.015), hypophosphatemia (OR = 57.00, P = 0.001), hypocalcaemia (OR = 23.22, P = 0.015) | DFX was stopped. Fluid and electrolyte supplementation. SCR was normalized. All features of proximal tubular dysfunction resolved. DFX was restarted. Normalized after reduction or withdrawal of DFX. |
| Tunc et al, 2012 [88]   | Cohort study, single center, evaluating the incidence of DFX-related adverse events. | 8 patients with Fanconi anemia aged 12.8 ± 3.6 years old | All patients were receiving oxymethalone. | 10–30 mg/kg/d for 13.6 ± 5.8 months | Proteinuria (87.5%). Increase in SCR (37.5%) in: a patient with unilateral renal agenesis (from 1.03 mg/dl to 1.44 mg/dl), a patient who undergone surgery for cellulitis (SCR 1.28 mg/dl), a patient with congenital abnormality of the right | SCR was normalized in 2/3 of patients after transient cessation of DFX. Other information is not provided. |

(Continued)
| Authors                  | Study design | Patient population | Comorbidities/other potentially nephrotoxic medications | Dose and duration of treatment | Clinical picture                                                                                                                                                                                                 | Outcome                                                                                   |
|-------------------------|--------------|--------------------|---------------------------------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Rheault et al, 2011 [82]| Two case reports | 7.5-year-old male with TDT | None | 30 mg/kg/d for 18 months. | Normal-anion gap metabolic acidosis, hypokalemia, phosphaturia, glucosuria, aminoaciduria, hypercalciuria. Elevated protein to creatinine ratio (0.38), urine calcium to creatinine ratio (0.46) and urine β2M. | DFX was stopped. Fluid and electrolyte supplementation. Features FS were improved. DFX was restarted at 20 mg/kg/d with evidence of mild FS (elevated urine β2M, hypercalciuria). Stable without intervention. |
| Wei et al, 2011 [83]    | Case report   | 18.75-year-old male with TDT | Secondary hypothyroidism and hypogonadotropic hypogonadism/oral thyroxine, intramuscular testosterone cypionate | None | 30 mg/kg/day for 12 months. | Elevated protein to creatinine ratio (0.38), urine calcium to creatinine ratio (0.46) and urine β2M. Proteinuria, glycosuria, hypophosphatemia, hypocalcemia, hypopatremia, hypokalemia, metabolic acidosis, low serum uric acid, elevated urinary β2M. Increase in SCr from 0.5–1.74 mg/dL. Also developed coma, hepatic dysfunction and thrombocytopenia. | Fluid and electrolyte supplementation. DFX was stopped and patient had full recovery. |
| Yacobovich et al, 2010 [84] | Four case reports | 8.5-year-old female with TDT | None | 30 mg/kg/d for 8 months. | Metabolic acidosis, glycosuria, hypokalemia, hypophosphatemia, hypophosphatemia. | DFX was stopped. Fluid and electrolyte supplementation. FS was resolved. |
|                        |              | 11-year-old female with TDT | None | 30 mg/kg/d for 24 months. | Metabolic acidosis, glycosuria, hypokalemia, hypophosphatemia, hypophosphatemia. | DFX was stopped. Fluid and electrolyte supplementation. FS was resolved. |
|                        |              | 8-year-old male with TDT | None | 30 mg/kg/d for 36 months. | Metabolic acidosis, glycosuria, hypokalemia, hypophosphatemia, hypophosphatemia. | DFX was stopped. Fluid and electrolyte supplementation. FS was resolved. |
|                        |              | 32-year-old female with TDT | Calcium plus vitamin D supplement. Also, on ofloxacin and phenazopyridine HCL for a recently diagnosed urinary tract infection | None | 38 mg/kg/d for 33 months. | Metabolic acidosis, glycosuria, hypokalemia, hypophosphatemia, hypophosphatemia, kaliuriis. | DFX was stopped. Fluid and electrolyte supplementation. FS was resolved. |
| Grange et al, 2010 [78] | Case report   | 77-year-old male with non-hereditary hemochromatosis. | Hypertension/irbesartan, HCTZ, ursodesoxycholic acid | 1500 mg/day for 1 month. | Glycosuria, hypokalemia, hypophosphatemia, hypocalcemia, kaliuriis, phosphaturia, aminoaciduria. Increase in SCr at 180 μmol/L. | DFX was stopped. Fluid and electrolyte supplementation. FS was resolved. SCr was normalized. |
| Even-Or et al, 2009 [77] | Two case reports | 18-year-old male with pure red cell aplasia. | None. | 20 mg/kg/d for 6 months. | Glycosuria, uricosuria, phosphaturia, kaliuriis, aminoaciduria, low serum uric acid, hypophosphatemia, hypophosphatemia. Increase in SCr from 0.6–1.07 mg/dL. | DFX was stopped. Fluid and electrolyte supplementation. FS and SCr were resolved. DFX was restarted and mild hypouricemia, hypophosphatemia, phosphaturia and increased urinary β2M within a few weeks, while on 10 mg/kg/day of DFX. He continued treatment with increasing doses with no further deterioration. |
|                        |              | 11-year-old female with TDT. | Acute graft rejection after AHSC at the age of 4 years, splenectomy. | 30 mg/kg/d for 6 months. | Glycosuria, uricosuria, phosphaturia, kaliuriis, aminoaciduria, low serum uric acid, hypophosphatemia, hypophosphatemia, increased urinary β2M | DFX was stopped. Electrolyte supplementation. FS was resolved. |

Note: DFX: Deferasirox; FS: Fanconi syndrome; SCr: Serum creatinine; DBA: Diamond-Blackfan anemia; β2M: β2 microglobulin; HCTZ: Hydrochlorothiazide; AHSC: Allogeneic hematopoietic stem cell transplantation.
thalassemia patients with end stage renal disease [93] or diabetes mellitus [94].

DFO chelates iron is located in plasma and ferritin by forming a metabolically inactive complex, which is renally excreted. DFO is poorly absorbed by the oral route. Consequently, intravenous or subcutaneous administration is required [95]. Acute renal failure necessitating dialysis following intravenous DFO overdose was described in patients who received 10-times the recommended dose due to administration pump failure [96] or with inadequate monitoring [67]. Similarly to DFX, transient and within the normal range serum creatinine increase has been documented in 14% of patients receiving DFO [85], whereas the same agent was also associated with increased level of NAG and tubular dysfunction in patients with TM [97]. It is important to note that DFO poses a risk of Yersinia, mucormycosis (zygomycosis) and Vibrio vulnificus infection and sepsis [98–100], an additional factor that causes acute kidney injury if left untreated.

The mechanisms involved in GFR alteration concurrently with iron depletion include impaired mitochondrial function and consequent production of adenosine and adenosine triphosphate, that leads to the activation of the tubulo-glomerular feedback and vasoconstriction of the afferent glomerular arterioles. Interference with prostaglandin production and imbalance between vasodilating and vasoconstrictive substances is also implicated in GFR reduction [67].

The management of serum creatinine elevation should be individualized based on the magnitude of increase and the presence of additional risk factors for renal disease or comorbid conditions. Recommendations for dose modifications and monitoring in patients who experience DFX- associated adverse events are available [101].

In conclusion, this narrative review highlights the most common pathophysiological and clinical manifestations of renal disease in beta-thalassemia patients. There is a need for close monitoring and follow up of renal function both in NTDT and TDT patients as their life expectancy has increased and this puts them potentially at increased risk of sever renal disease. More longitudinal data is required to fully portray any differences in renal disease in TDT and NTDT patients, as well as the current prevalence of this comorbidity in the era of new iron chelation and blood transfusion guidelines.

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No potential conflict of interest was reported by the authors.

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References
[1] Yesilipek MA. Stem cell transplantation in hemoglobinopathies. Hemoglobin. 2007;31:251–256.
[2] Rivella S. Beta-thalassemias: paradigmatic diseases for scientific discoveries and development of innovative therapies. Haematologica. 2015;100:418–430.
[3] Shinar E, Rachmilewitz EA. Oxidative denaturation of red blood cells in thalassemia. Semin Hematol. 1990;27:70–82.
[4] Yuan J, Kannan R, Shinar E, et al. Isolation, characterization, and immunoprecipitation studies of immune complexes from membranes of beta-thalassemic erythrocytes. Blood. 1992;79:3007–3013.
[5] Origa R. Beta-thalassemia. Genet Med. 2017;19:609–619.
[6] Deloughery TG. Microcytic anemia. N Engl J Med. 2014;371:2537.
[7] Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood. 2010;115:4331–4336.
[8] Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86:480–487.
[9] Ginzburg Y, Rivella S. Beta-thalassemia: a model for elucidating the dynamic regulation of ineffective erythropoiesis and iron metabolism. Blood. 2011;118:4321–4330.
[10] Quinn CT, Johnson VL, Kim HY, et al. Thalassemia clinical research N. renal dysfunction in patients with thalassemia. Br J Haematol. 2011;153:111–117.
[11] Yaghobi M, Mirmohaddam E, Majid N, et al. Complications of transfusion-dependent beta-thalassemia patients in Sistan and Baluchistan, South-East of Iran. Int J Hematol Oncol Stem Cell Res. 2017;11:268–272.
[12] Mokhtar GM, Gadallah M, El Sherif NH, et al. Morbidities and mortality in transfusion dependent beta-thalassemia patients (single-center experience). Pediatr Hematol Oncol. 2013;30:93–103.
[13] Ong-ajyouth P, Ong-ajyouth S, et al. Renal function in adult beta-thalassemia/Hb E disease. Nephron. 1998;78:156–161.
[14] Ahmadzadeh A, Jalali A, Assar S, et al. Renal tubular dysfunction in pediatric patients with beta-thalassemia major. Saudi J Kidney Dis Transpl. 2011;22:497–500.
[15] Sadeghi-Bojd S, Hashemi M, Karimi M. Renal tubular function in patients with beta-thalassemia major in Zahedan, Southeast Iran. Singapore Med J. 2008;49:410–412.
[16] Sen V, Ece A, Uluca U, et al. Urinary early kidney injury molecules in children with beta-thalassemia major. Ren Fail. 2015;37:607–613.
[17] Patsaoura A, Tatsi E, Margeli A, et al. Plasma neutrophil gelatinase-associated lipocalin levels are markedly increased in patients with non-transfusion-dependent thalassemia: Lack of association with markers of erythropoiesis, iron metabolism and renal function. Clin Biochem. 2014;47:1060–1064.
[18] Roudkenar MH, Halabian R, Oodi A, et al. Upregulation of neutrophil gelatinase-associated lipocalin, NGAL/Lcn2, in betathalassemia patients. Arch Med Res. 2008;39:402–407.
[19] Aldudak B, Karabay Bayazit A, Noyan A, et al. Renal function in pediatric patients with beta-thalassemia major. Pediatr Nephrol. 2000;15:109–112.
[20] Moham M, Shamsian BS, Gharib A, et al. Early markers of renal dysfunction in patients with beta-thalassemia major. Pediatr Nephrol. 2008;23:971–976.

[21] Smolkin V, Halevy R, Levin C, et al. Renal function in children with beta-thalassemia major and thalassemia intermedia. Pediatr Nephrol. 2008;23:1847–1851.

[22] Sumboonnanonda A, Malasit P, Tanphaichitr VS, et al. Renal tubular function in beta-thalassemia. Pediatr Nephrol. 1998;12:280–283.

[23] Zhou XJ, Laszik Z, Wang XQ, et al. Association of renal injury with increased oxygen free radical activity and altered nitric oxide metabolism in chronic experimental hemosiderosis. Lab Invest. 2000;80:1905–1914.

[24] Michelakakis H, Dimitriou E, Georgakis H, et al. Iron overload and urinary lysosomal enzyme levels in beta-thalassaemia major. Eur J Pediatr. 1997;156:602–604.

[25] Koliakos G, Papachristou F, Koussi A, et al. Urine biochemical markers of early renal dysfunction are associated with iron overload in beta-thalassaemia. Clin Lab Haematol. 2003;25:105–109.

[26] Hashemieh M, Azarkeivan A, Akhlaghpour S, et al. T2-star (T2*) magnetic resonance imaging for assessment of kidney iron overload in thalassemic patients. Arch Iran Med. 2012;15:91–94.

[27] Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17:17–25.

[28] Nagababu E, Gulyani S, Earley CJ, et al. Iron-deficiency anaemia enhances red blood cell oxidative stress. Free Radic Res. 2008;42:824–829.

[29] Manotham K, Tanaka T, Matsumoto M, et al. Transdifferentiation of cultured tubular cells induced by hypoxia. Kidney Int. 2004;65:871–880.

[30] Norman JT, Clark IM, Garcia PL. Hypoxia promotes fibrogenesis in human renal fibroblasts. Kidney Int. 2000;58:2351–2366.

[31] Norman JT, Orphanides C, Garcia P, et al. Hypoxia-induced changes in extracellular matrix metabolism in renal cells. Exp Nephrol. 1999;7:463–469.

[32] Tantawy AA, El Bablawy N, Adly AA, et al. Early predictors of renal dysfunction in Egyptian patients with beta-thalassemia major and intermedia. Mediterr J Hematol Infect Dis. 2014;6:e2014057.

[33] Sumboonnanonda A, Sanpakit K, Piyaphanee N. Renal function and urinary markers of early renal dysfunction are associated with iron overload in beta-thalassaemia. Pediatr Nephrol. 2008;23:1847–1851.

[34] Davis LE, Hohimer AR. Hemodynamics and organ blood flow in fetal sheep subjected to chronic anemia. Am J Physiol. 1991;261:R1542–R8.

[35] Lafferty HM, Anderson S, Brenner BM. Anemia: a potent modulator of renal hemodynamics in models of progressive renal disease. Am J Kidney Dis. 1991;17:2–7.

[36] Hostetter TH. Hyperfiltration and glomerulosclerosis. Semin Nephrol. 2003;23:194–199.

[37] Alfrey AC. Role of iron and oxygen radicals in the progression of chronic renal failure. Am J Kidney Dis. 1994;23:182–187.

[38] Musallam KM, Taher AT. Mechanisms of renal disease in beta-thalassemia. J Am Soc Nephrol. 2012;23:1299–1302.

[39] Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34:571–590.

[40] Levey AS, Coresh J, Greene T, et al. Chronic kidney disease epidemiology Collaboration. using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–254.

[41] Milo G, Feige Gross Nevo R, Pazgal I, et al. GFR in patients with beta-thalassemia major. Clin J Am Soc Nephrol. 2015;10:1350–1356.

[42] Economidou M, Printza N, Teli A, et al. Renal dysfunction in patients with beta-thalassemia major receiving iron chelation therapy either with deferoxamine and deferiprone or with deferasirox. Haematol. 2010;123:148–152.

[43] Hamed EA, Elmeglly NT. Renal functions in pediatric patients with beta-thalassemia major: relation to chelation therapy: original prospective study. Ital J Pediatr. 2010;36:39.

[44] Al-Khabori M, Bhandari S, Al-Rasadi K, et al. Correlation of iron overload and glomerular filtration rate estimated by cystatin C in patients with thalassemia major. Haemoglobin. 2014;38:365–368.

[45] Piga A, Fraccchia S, Lai ME, et al. Deferasirox effect on renal haemodynamic parameters in patients with transfusion-dependent beta thalassaemia. Br J Haematol. 2015;168:882–890.

[46] Lai ME, Spiga A, Vaccquer S. Renal function in patients with beta-thalassemia major: a long-term follow-up study. Nephropathy, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2012;27(9):3547–3598.

[47] Deveci B, Kurtoglu A, Kurtoglu E, et al. Documentation of renal glomerular and tubular impairment and glomerular hyperfiltration in multi-transfused patients with beta thalassemia. Ann Hematol. 2016;95:375–381.

[48] Shapira Y, Glick B, Finsterbush A, et al. Myopathological findings in thalassemia major. Eur Neurol. 1990;30:324–327.

[49] Logothetis J, Constantoulakis M, Economidou J, et al. Thalassemia major (homozygous beta-thalassemia). A survey of 138 cases with emphasis on neurologic and muscular aspects. Neurology. 1972;22:294–304.

[50] Levey AS. Measurement of renal function in chronic renal disease. Kidney Int. 1990;38:167–184.

[51] Shemesh O, Golbetz H, Kriss JP, et al. Limitations of serum creatinine as a filtration marker in glomerulopathic patients. Kidney Int. 1985;28:830–838.

[52] Filler G, Huang SH, Yasin A. The usefulness of cystatin C and related formulae in pediatrics. Clin Chem Lab Med. 2012;50:2081–2091.

[53] Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40:221–226.

[54] Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51:395–406.
[95] Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med. 2011;364:146–156.

[96] Prasannan L, Flynn JT, Levine JE. Acute renal failure following deferoxamine overdose. Pediatr Nephrol. 2003;18:283–285.

[97] Aydinok Y, Coker C, Kavakli K, et al. Urinary zinc excretion and zinc status of patients with beta-thalassemia major. Biol Trace Elem Res. 1999;70:165–172.

[98] Adamkiewicz TV, Berkovitch M, Krishnan C, et al. Infection due to Yersinia enterocolitica in a series of patients with beta-thalassemia: incidence and predisposing factors. Clin Infect Dis. 1998;27:1362–1366.

[99] Chan GC, Chan S, Ho PL, et al. Effects of chelators (deferoxamine, deferiprone and deferasirox) on the growth of Klebsiella pneumoniae and Aeromonas hydrophila isolated from transfusion-dependent thalassemia patients. Hemoglobin. 2009;33:352–360.

[100] Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. J Clin Invest. 1993;91:1979–1986.

[101] Vichinsky E. Clinical application of deferasirox: practical patient management. Am J Hematol. 2008;83:398–402.