Mechanisms of Renal Disease in β-Thalassemia

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ABSTRACT

Although advances in the care of patients with β-thalassemia translate into better patient survival, this success has allowed previously unrecognized complications to emerge, including several renal abnormalities. Clinical studies continue to show that mild tubular dysfunction and abnormalities in GFR are common in patients with β-thalassemia. Chronic anemia and iron overload are believed to lie behind these abnormalities. Nonprogressive increases in levels of serum creatinine have also been observed after exposure to some iron chelators. Longitudinal studies are needed to understand the true burden of renal dysfunction in patients with β-thalassemia.


As a group, the thalassemias are the most common monogenic disorders worldwide, presenting a significant public health concern for developing countries. Large migrations from countries where the disease is prevalent have also increased the number of patients in multiethnic western cities. β-thalassemia is an inherited disorder of hemoglobin synthesis wherein mutations of the β-globin gene lead to various degrees of defective β-chain production, an imbalance in α/β-globin chain synthesis, ineffective erythropoiesis, and a spectrum of anemia.

Patients with β-thalassemia major present in the first year of life with profound anemia and subsequently require regular blood transfusions for survival, as well as iron chelation therapy to treat transfusional iron overload and prevent end-organ damage. Some patients, however, present later in life with a milder form of anemia (hemoglobin level, 70–90 g/L) and remain largely transfusion-independent: the so-called β-thalassemia intermedia phenotype. Patients with β-thalassemia intermedia can also develop considerable iron overload due to increased intestinal iron absorption triggered by the ongoing ineffective erythropoiesis. Chronic anemia, iron overload, and the use of specific iron chelators have all been linked to renal manifestations in patients with β-thalassemia.

Evidence of proximal tubular damage is observed in patients with β-thalassemia major. Low-molecular-weight proteinuria is found in almost all patients. Moreover, several studies report increased urinary excretion of several markers of proximal tubular damage in a considerable number of patients with β-thalassemia major, including N-acetyl-β-D-glucosaminidase and β₂-microglobulin (up to 60%); calcium (approximately 13%), phosphate and magnesium (about 9%), uric acid (30%–40%), amino acids (approximately 30%), and malondialdehyde derived from the destruction of membrane lipids by peroxidation. A more recent study shows that the secretion of such markers is significantly reduced in patients with β-thalassemia major who have undergone curative hematopoietic stem-cell transplantation compared with age-matched patients who have not had transplantation.

Both iron overload and chronic anemia could explain tubular dysfunction in patients with β-thalassemia, although the two often coexist and the independent contribution of each risk factor has not been widely investigated. Rats subjected to chronic iron loading develop iron deposits that are clearly evident in glomeruli and in proximal but not distal tubules, as well as signs of significant glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Autopsy series of patients with β-thalassemia major show hemosiderin deposits in both the terminal portion of proximal tubules and the distal tubules. In the acidic proximal tubular fluid, iron dissociates from transferrin, resulting in the production of reactive oxygen species with subsequent damage to the brush border of the renal tubular membrane. If iron enters proximal tubular cells along with transferrin, it can be released from transferrin inside the lysosomes to enter the cytoplasm as free reactive iron, where it also stimulates the production of reactive oxygen species and cellular injury. The mechanism of injury is mediated by mitochondrial stress in proximal tubular cells, as evidenced by increased efflux of cytochrome C, release of lactate...
dehydrogenase, and reduction in adenosine triphosphate. This pathologic and experimental evidence is supported by clinical studies showing a good correlation between serum ferritin levels and markers of tubular toxicity, and by reversal of tubular defects after iron chelation therapy. Chronic anemia and hypoxia are also associated with oxidative stress, lipid peroxidation, and functional abnormalities in tubular cells. Damage to the proximal tubule and volume increases of the peritubular space were also demonstrated in one study on anemic rats. A good correlation between the severity of anemia and markers of tubular abnormalities are reported in patients with \( \beta \)-thalassemia major.

Abnormalities in GFR are also evident in patients with \( \beta \)-thalassemia. In patients with \( \beta \)-thalassemia who do not receive regular transfusion therapy (patients with \( \beta \)-thalassemia intermedia), creatinine clearance and GFR are increased. Anemia may reduce systemic vascular resistance, leading to a hyperdynamic circulation that increases renal plasma flow and GFR. These changes can eventually lead to stretching of the glomerular capillary wall and subsequent endothelial and epithelial injury, together with transudation of macromolecules into the mesangium associated with glomerular dysfunction. In the long-term, such changes may lead to a progressive decline in GFR. Moreover, chronic hypoxia of tubular cells with increased metabolic demand causes apoptosis or epithelial-mesenchymal transition, leading to the development of tubulointerstitial injury and consequent glomerulosclerosis and kidney fibrosis.

In addition, tubular cell damage from heavy iron overload may allow injured cells to migrate into the interstitium, releasing cytokines and growth factors that can cause tubulointerstitial scarring and glomerular sclerosis and leading to further decrease in GFR. A negative correlation between serum ferritin levels and GFR, evident from measurement of cystatin C, has been reported in patients with \( \beta \)-thalassemia major. Additional factors that contribute to a decreased GFR in these patients include transfusion-related hepatitis B or C virus or HIV infections leading to GN, as well as iron-induced hepatic and cardiac dysfunction.

Three iron chelators are available for the management of iron overload in \( \beta \)-thalassemia: parenteral deferoxamine mesylate (Desferal, Novartis) and the oral agents deferiprone (Ferroprox, Apotex; Kelfer, Cipla) and deferasirox (Exjade, Novartis) (Table 1). Renal manifestations attributed to iron chelation therapy have probably received the most attention from investigators studying thalassemia. Acute renal failure attributed to drug use is rare but has also been reported. In some studies, deferoxamine overdose secondary to administration-pump malfunction or inadequate dosage monitoring resulted in acute renal failure necessitating dialysis. Findings on renal biopsy describe tubular necrosis, which is the most likely cause given the reversible nature of damage.

Several cases of acute kidney injury have also been reported in postmarketing surveillance of the oral chelator deferasirox. Recently, a boxed warning was added to the deferasirox prescribing information in the United States, although this amendment has not been adopted by the European Health Authority or applied globally. The warning indicates the drug may cause renal and hepatic impairment, including failure and gastrointestinal hemorrhage. In some cases, these reactions were fatal. However, such reactions were more frequently observed in patients with advanced age, high-risk myelodysplastic syndromes, underlying renal or hepatic impairment, or low platelet counts.

### Table 1. Available iron chelators for the management of transfusional iron overload in patients with \( \beta \)-thalassemia

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dosage Route</td>
<td>25–60 mg/kg per day Subcutaneous/ intravenous 8–12 hr, 5 d/wk</td>
<td>75 mg/kg per day Oral, 3 times daily</td>
<td>20–40 mg/kg per day Oral, once daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 min</td>
<td>3–4 h</td>
<td>8–16 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, fecal Urinary Decreased cardiac mortality, especially in combination with deferoxamine</td>
<td>Economic</td>
<td>Ease of administration</td>
</tr>
<tr>
<td>Advantages</td>
<td>Improved survival in adherent patients</td>
<td>Increased appetite/ weight gain</td>
<td>Significant reduction in hepatic and cardiac siderosis</td>
</tr>
<tr>
<td>Adverse events common</td>
<td>Local injection site reactions</td>
<td>Reddish-brown urine</td>
<td>GI disturbances</td>
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<tr>
<td>GI disturbances</td>
<td>GI disturbances</td>
<td>GI disturbances</td>
<td>Increased serum creatinine levels</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>Increased appetite/ weight gain</td>
<td>Agranulocytosis</td>
<td>Rash</td>
</tr>
<tr>
<td>rare</td>
<td>Ophthalmologic changes</td>
<td>Agranulocytosis</td>
<td>Aminotransferase elevations</td>
</tr>
<tr>
<td>Auditory disturbance</td>
<td>Neutropenia</td>
<td>Aminotransferase elevations</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Aminotransferase elevations</td>
<td>Aminotransferase elevations</td>
<td>Arthralgia</td>
<td>Renal and hepatic failure</td>
</tr>
<tr>
<td>Bone abnormalities</td>
<td>Arthralgia</td>
<td>Progression of liver fibrosis</td>
<td>GI hemorrhage</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>Neurologic disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>Respiratory distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Neurologic disturbance</td>
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</table>

GI, gastrointestinal.
Fluctuations in levels of serum creatinine with deferasirox therapy have also been the subject of concern. In a multicenter randomized phase 3 registration trial comparing deferasirox and deferoxamine therapy in patients with β-thalassemia major, mild, dose-dependent increases in serum creatinine were observed in 38% of patients receiving deferasirox at dosages of 20–30 mg/kg per day. These increases were sometimes transient, were mostly within the normal range, and did not exceed twice the upper limit of normal. Dose reductions were required in only 13% of patients receiving deferasirox. In about 25% of these patients, levels of serum creatinine returned to baseline, and in the remainder of patients it remained stable or fluctuated between baseline and the maximum increase observed before dose reduction.27 Safety data with deferasirox in children and adults with β-thalassemia major have now been reported for up to 5 years of treatment and confirm absence of progressive increases in serum creatinine over longer-term treatment,28 even in patients with heavy iron load who require dose escalation to >30 mg/kg per day.29 Studies on levels of cystatin C in patients with β-thalassemia major receiving deferasirox for up to 9 months also confirm that changes are stable over the treatment period.25

The causes of this mostly reversible nonprogressive increase in serum creatinine in patients treated with deferasirox are still controversial. It has been hypothesized that the underlying mechanism is related not to a nephrotoxic effect of the drug itself but to overchelation leading to a relative depletion of iron and reduction in GFR.4 This hypothesis stems from observations of a similarly high rate of serum creatinine increase in the deferoxamine group (14% in patients with β-thalassemia major and 22% in those with sickle cell disease) during the randomized trials,27,30 and the fact that increases in serum creatinine are more common in patients who showed dramatic decreases in liver iron concentration and serum ferritin level or those with lower transfusion rate and baseline iron indices.27

The mechanisms used in alterations of the GFR with relative iron depletion include damage to mitochondrial function in tubular cells and production of adenosine and adenosine triphosphate (leading to activation of the tubuloglomerular feedback, vasoconstriction of the afferent preglomerular arterioles, and consequent reduction of GFR), and interference with the arachidonic acid cascade and the final production of prostaglandins (leading to an imbalance between vasodilating and vasoconstrictive prostaglandins, with consequent changes in intrarenal hemodynamics and GFR).4 In all cases, management of increases in serum creatinine should be individualized, although recommendations for dose reductions and monitoring are available.31 The search for novel iron chelators with more favorable renal safety profiles is ongoing.32

Despite expanding knowledge of renal manifestations in patients with β-thalassemia (Figure 1), it should be noted that most available studies are cross-sectional and involve a small number of patients. Longitudinal studies investigating the true incidence, mechanisms, and consequences of renal abnormalities in this patient population are warranted. Investigations involving transfusion-independent patients with β-thalassemia intermedia are also called for because data in this latter group are lacking.

**ACKNOWLEDGMENTS**

We would like to thank Professor Claudio Ponticelli (Division of Nephrology, Humanitas Scientific Institute, Milan, Italy) for insightful interpretations of the mechanisms of renal function in patients with β-thalassemia.

**Figure 1.** Mechanisms of renal disease in patients with β-thalassemia.
DISCLOSURES

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REFERENCES