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# Highlights on Deferasirox Use and its Renal Toxicity in Children with Beta Thalassemia Major

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## ABSTRACT

**Background:** Thalassemia is a hereditary disorder due to imbalance between α/β-globin chains. This leads to early hemolysis. It is of two type, α and β-thalassemia which is more sever needs lifelong follow up, treatment, by RBCs transfusion, to compensate for the drop in hemoglobin. This leads to increased iron stores and overload, excess iron deposited in different organs and kidneys. This leads to overproduction of free radicals; that causes organ damages.

**Objectives:** This study aimed to highlight the prevalence of renal injury in patients with β -thalassemia major, comparing subcutaneous and new oral iron chelating agents, and their effects on the renal functions.

**Patients and methods**: This case control and observational study included a total of 60 thalassemia major patients aged between 5 and 24 years who were following up at the Hematology Outpatient Clinic, Department of Pediatrics, Cairo University Hospitals. All patients were regularly transfused and receiving regular chelation program. Patients were divided between three groups.

**Results:** There were no significant differences between the three groups regarding glomerular filtration rate ($p > 0.05$), and between Deferiprone and Deferoxamine groups regarding the age, serum ferritin, serum cystatin C and urinary $\beta_2$-MG ($p > 0.05$). There were significant differences between Deferasirox group and both Deferiprone and Deferoxamine groups regarding serum ferritin, serum cystatin C and Urinary $\beta_2$-MG ($p < 0.05$).

**Conclusion:** Younger patients who are on iron chelation therapy with deferasirox needs regular assessment of renal dysfunction markers as having relatively higher levels of serum ferritin, serum cystatin C and urinary $\beta_2$-MG**.**

**Keywords:** Thalassemia, Deferasirox, nephrotoxicity,

## INTRODUCTION

An autosomal recessive illness called beta thalassemia is defined by an imbalance (reduction) in the production of the beta strand of hemoglobin, which results in early hemolysis, significant anemia, and continuous, lifelong blood transfusions to enhance general health [(1)].

Multiple organs, including the kidneys, experience iron deposition because of frequent, repeated blood transfusions; hence, iron chelation therapy must be initiated to reduce iron load and associated morbidity [(1)].

Thalassemia patients may experience renal dysfunction as of DFO side effects, iron deposition in the kidney, or other causes such as lipid peroxidation, stress oxidation, generation of free radicals, and thrombosis [(2,3)] release free radicals and thrombosis [(3)].

The aim of the current work was to highlight and detect the early renal involvement and the value of new bio markers of renal involvement, for example serum cystatin C and urine β2-microglobulin (β2-MG) ([4,5]).

## MATERIALS AND METHODS

This case control and observational study included a total of 60 thalassemia major patients aged between 5 and 24 years who were following up at the Hematology Outpatient Clinic, Department of Pediatrics, Cairo University Hospitals. All patients were regularly transfused and receiving regular chelation program.

This study was conducted between May, 2016 and May, 2017.

The included participants were divided into three groups; **Group I (Deferasirox)** included 14 patients maintained on deferasirox, **Group II (Deferiprone)** included 27 patients maintained on Deferiprone, and **Group III (control)** included 19 patients maintained on Deferoxamine.

### Inclusion criteria

Beta-thalassemia major patients aged from 5 to 24 years who were on regular blood transfusion and receiving regular chelation programs.

### Exclusion criteria

1- Patients with history suggestive of recurrent urinary tract infections.
2- Patients who had any chronic kidney disease or chronic systemic illness.
3- Patients with history of any nephrotoxic drug use.

### All the patients enrolled in the study were subjected to the following:

Comprehensive history taking with stress on: History including personal items like age, sex, duration, and volume of blood given as well as type of iron chelation therapy and the figure of mean serum ferritin levels of a 1-year period prior to the study.

- Comprehensive general and local examination
- Laboratory investigations including:

1. Blood samples for hematological, biochemical, and metabolic tests including total bicarbonates,



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urea, creatinine (Cr), potassium, sodium, magnesium, calcium, and phosphate.
2. Urine samples were obtained over the course of 24 hours to determine albumin, calcium, phosphorus, salt, and Cr.
3. Urine analysis to detect proteins, glucose, or RBCs and to determine the specific gravity.
4. Assessment of urinary 2-MG in a fresh urine sample and serum cystatin C (Cys C), which served as early indicators of renal and tubular failure, respectively.

***Ethical Consideration*:**

This study was ethically approved by Cairo University's Research Ethics Committee. Written informed consent of all the participants or the participants' parents was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

**Statistical analysis**

SPSS software for Windows, version 22.0 (IBM, Armonk, NY, USA), was used to analyse the data. Categorical data were given as numbers and percentages, and their analysis using the Chi square (2) and Fisher's exact tests, assuming normality at P>0.05. While non-parametric variables were presented as median and inter-quartile range (IQR), they were analyzed by Mann Whitney U test or Kruskal Wallis (KW) test for two or more independent groups, respectively.

**RESULTS**

This research was done on 60 thalassemia patients. All the patients had regular chelation treatments and transfusions.

No significant differences were detected between three groups regarding glomerular filtration rate (p> 0.05) and between Deferiprone and Deferoxamine groups regarding the age, serum ferritin, serum cystatin C and Urinary $\beta_2$-MG (p> 0.05). However, there were significant differences between Deferasirox group and both Deferiprone and Deferoxamine groups regarding the age, serum ferritin, serum Cystatin C and Urinary $\beta_2$-MG (p< 0.05).

**Table (1):** Characteristics of the iron chelation therapy groups of studied patients.

| | **Deferasirox ( n = 14 )** | **Deferiprone ( n = 27 )** | **Deferoxamine ( n = 19 )** | **P** **P1** **P2** **P3** |
|---|---|---|---|---|
| **Age (Years)** X±SD | 9.36±0.19 | 16.44±1.84 | 17.05±1.59 | 0.001 0.001 |
| Range | (5-14) | (10-24) | (9-24) | NS |
| **Serum ferritin (ng/ml)** X±SD | 3312.3±183.4 | 2697.5±97 | 2782.9±89 | 0.01 0.01 NS |
| **eGFR** (mL/min/1.73m$^2$) X±SD | 124.36±8.21 | 118.33±6.14 | 120.17±7.34 | NS NS NS |
| **Serum Cystatin C (mg/l)** X±SD | 0.98±0.15 | 0.87±0.17 | 0.90±0.15 | 0.03 0.01 NS |
| **Urinary $\beta_2$-MG (mg/l)** X±SD | 4.01±0.67 | 2.16±0.53 | 2.24±0.21 | 0.001 0.001 NS |
| Range | | | | |

*P1= Deferasirox group VS Deferiprone group
P2= Deferasirox group VS Deferoxamine group
P3= Deferiprone group VS Deferoxamine group

Figures 1,2,3, and 4 demonstrate the characteristics of the iron chelation therapy among groups of studied patients. There were significant differences between Deferasirox group and both Deferiprone and Deferoxamine groups regarding the age, serum ferritin, serum Cystatin C and Urinary $\beta_2$-MG (p< 0.05).

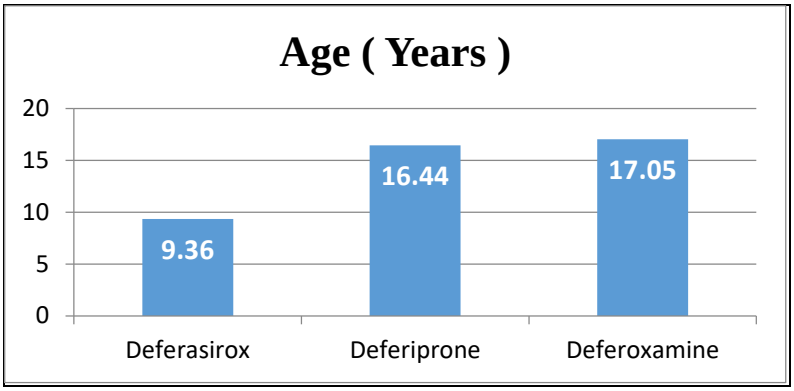


**Figure (1):** The mean age of the iron chelation therapy groups.

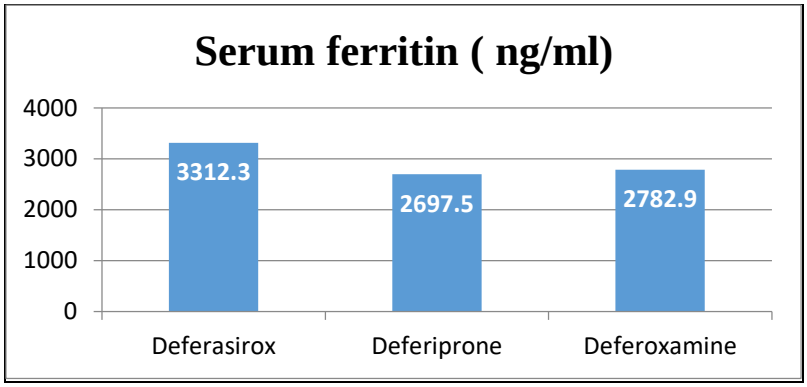


**Figure (2):** The mean serum ferritin of the iron chelation therapy groups.

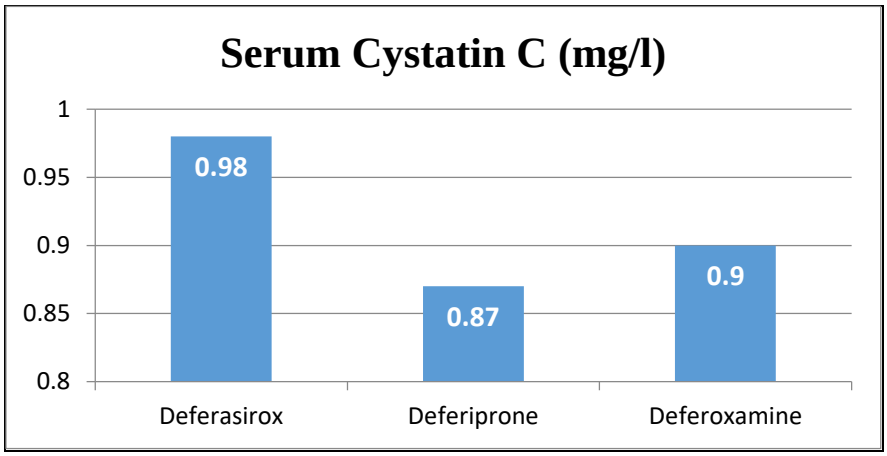


**Figure (3):** The mean serum Cystatin C of the iron chelation therapy groups.

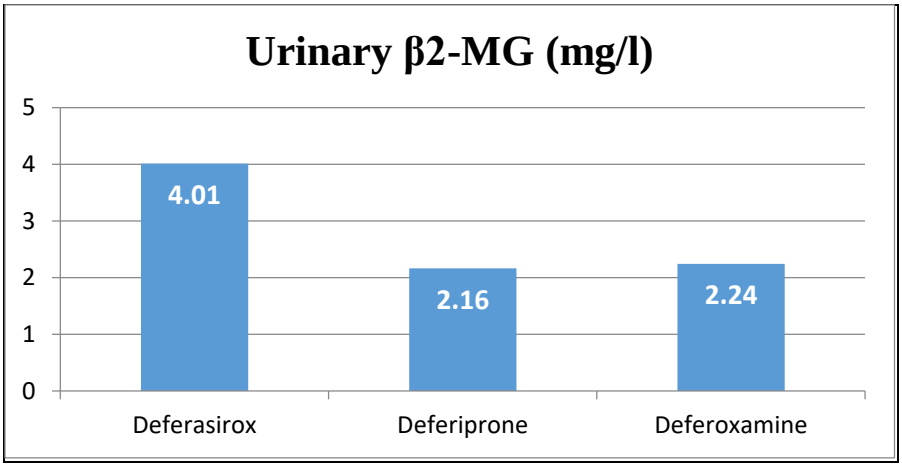


**Figure (4):** The mean urinary $\beta_2$-MG of the iron chelation therapy groups.

## DISCUSSION

In this study, thalassemic patients were classified into two age groups: 5-10 years (14 patients) and >10 years (46 patients). We have found non-significant differences between both groups in hemoglobin concentration, urea, creatinine, and glomerular filtration rate (p> 0.05). On the other hand, serum ferritin, serum Cystatin C and Urinary $\beta_2$-MG were significantly higher in the younger age group (p< 0.05).

The younger age group had substantially increased levels of cystatin C and urinary 2-MG (p 0.05). Another study, **Economou *et al.*** [6] found that kidney affection seems to occur even in young beta-thalassemia patients, hence close follow up is advised for early detection of any kidney abnormality before fulminant renal failure

**Naderi *et al.*** [7] found in 30 β- thalassemic children who were at mean age of 4.9 ± 3.2 years a significant increase for the mean urinary β2-microglobulin (β2-MG). **Dee *et al.*** [8] reported that Deferasirox-associated renal tubular toxicity in the form of significant increase in the mean urinary β2-microglobulin (β2-MG) could be more prominent in young patients whose their tubules is not fully mature [9]

One of the mainstays of the treatment of chronic iron overload in thalassemia patients is use of iron chelators. Subcutaneous or Intravenous deferoxamine, oral deferiprone, and deferasirox are the main iron chelators that are currently accessible [10].

All three chelators have the potential to have an impact on renal function. Acute kidney injury (AKI) and mild transient elevations in blood creatinine are both glomerular dysfunctions. When greater doses and overdoses of deferoxamine were administered, up to 40% of patients experienced AKI and abrupt abnormalities in renal function [11].

Vomiting and diarrhea are frequent, and they can cause volume loss and pre-renal AKI [12]. It is well known if iron accumulation in the renal tubules it couldn't properly eliminated by iron chelation, and ferritin levels do not accurately indicate the degree of hemosiderosis. Ferritin was not discovered to be an has a direct relation for any renal dysfunction, according to **Economou *et al.*** [6], even though more than half of the patients they evaluated their ferritin levels higher than 1000 ng/ml.

**Piga *et al.*** [13] showed that patients with TM who received regular transfusions had normal GFR as determined by plasma sample of 51Cr EDTA, following 8 weeks of therapy with thirty mg/kg Deferasirox once a day; they displayed a drop in GFR of 9.5%, which fully recovered after a 2-week washout. They then gave equivalent care to five individuals for two years. In this instance, GFR dropped to 89.4 ml/min shortly after therapy started a 19.1 ml/min (17.7%) decline. After that, there was no further progressive deterioration, and after stoppage of Deferasirox medication stopped after two years, GFR returned to normal after a four-week clearance from the body

In this study, there were no significant differences while using the three iron chelation therapy groups regarding glomerular filtration rate (p > 0.05). There were also no significant differences between Deferiprone and Deferoxamine groups regarding the age, serum ferritin, serum Cystatin C and Urinary $\beta_2$-MG (p> 0.05). However, there were significantly higher levels of serum ferritin, serum Cystatin C and Urinary $\beta_2$-MG in the Deferasirox group as compared to the Deferiprone and Deferoxamine groups.

In previous studies by **Aldudak *et al.*** [2] and **Mohkam *et al.*** [14] on patients receiving DFO using common markers, early renal changes could not be demonstrated. As a result of chronic anemia, iron deposition, and/or drug like DFO cumulative toxicity, these studies have primarily shown the presence of proximal tubular compromise in those patients [2, 14]. **Papassotiriou *et al.*** [15] also reported slight changes of cystatin C level during deferasirox treatment in β-thalassemia population.

Thalassemia patients on deferasirox, **Naderi *et al.*** [7] showed a substantial rise in the mean urine levels of protein, uric acid, calcium, and magnesium (P >.05) . They emphasised the tubular nephropathy that Defera sirox causes in beta thalassemia patients also verified i mportance of careful anticipation of any kidney abnormality in those individuals.

18 patients with thalassemia who were receivin g iron chelation therapy on a regular basis,had not und ergone splenectomies, and had no prior history of renal disease were evaluated by**Deer *et al.*** [8] in their study. Nine patients (50%) were receiving deferasirox, three ( 16%) were receiving deferoxamine, two (11%) were re ceiving deferiprone, and four (22%) were receiving a combination of deferasirox and deferoxamine.

Twelve (66%) individuals, including all nine (5 0%) of the deferasirox patients, exhibited renal tub ular dysfunction. Half of patients had acquired renal tu bular abnormalities 12–13 months. Despite higher 2-MG (P: 0.003), patients on different chelation regimens had no electrolyte abnormality. The mean urine 2-microglobulin (2-MG) level for these 12 patients with renal tubular failure was 7 98 mg/l (range: 0 – 26 3 mg/l). In comparison to patients on other chelation regimens, they found that in a small cohort of mostly Oriental-thalassemic patients receiving deferasirox, asymptomatic renal tubular impairment was quite common. As Younger age group renal tubules may not fully mature, so they are liable to deferasirox-associated tubular damage. If caught early, it can be reversed by lowering the dosage or stopping the medication [10, 16].

## CONCLUSION

Younger patients who are on iron chelation therapy with deferasirox needs regular assessment of renal

dysfunction markers as having relatively higher levels of serum ferritin, serum cystatin C and Urinary $\beta_2$-MG**.**

**Conflict of interest**
The authors declare no conflict of interest.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Author contribution**
Authors contributed equally in the study.

**Ethical Approval**
Ethical approval was cleared by ethical committee Faculty of Medicine, Cairo University, Cairo, Egypt

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