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RESEARCH ARTICLE

Evaluating Renal Glomerular Function in Beta-Thalassemia Patients Receiving Deferasirox Using Serum Cystatin-C and Creatinine: A Cross-Sectional Study

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ABSTRACT

The introduction of iron chelation therapies has notably extended the life expectancy of individuals with β-thalassemia, thereby presenting the potential for the emergence of new complications such as renal impairments. Because creatinine levels are influenced by body mass and nutritional status, there is a need for a more sensitive and reliable indicator of renal glomerular function. Here, we studied 27 individuals with β-thalassemia undergoing iron chelation therapy with Deferasirox. The serum levels of cystatin-C, a highly sensitive biomarker for renal dysfunction, were quantified using an immunoturbidimetry assay. We subsequently analyzed the data, examining correlations with other clinical and laboratory parameters. We determined the glomerular filtration rate (GFR) using both creatinine and cystatin-C-based equations. According to the creatinine equation, none of the patients had a reduced GFR, but 59% exhibited a reduced GFR value based on the cystatin-C equation. Patients with elevated cystatin-C levels exhibited higher serum creatinine ($p<0.001$) and BUN ($p=0.002$) and lower ferritin ($p=0.023$) levels. Our study revealed a positive correlation between cystatin-C and creatinine ($p=0.002$), BUN ($p=0.018$), and BMI ($p=0.046$), while a negative correlation was observed with ferritin ($p=0.006$). We found no correlation between cystatin-C and age, weight, height, Deferasirox therapy duration, or blood transfusion frequency. Multiple regression analysis indicated that ferritin ($p=0.003$) significantly affected cystatin-C levels, while other variables did not. Additionally, no independent variables had a significant impact on creatinine levels. Since there is a high likelihood of subclinical renal impairment in these patients, we recommend regular monitoring of serum cystatin-C as a screening tool.

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KEYWORDS
Beta-thalassemia; renal function; cystatin-C; creatinine; Deferasirox

Introduction

Beta thalassemias, a heterogeneous group of autosomal recessive hereditary anemias, affect the production and processing of the β chain of hemoglobin. According to the World Health Organization (WHO), it impacts 40,000 fetuses annually, and 25,000 of them will require blood transfusions in the future. The quality of life of β-thalassemia patients is affected by complications resulting from chronic hypoxia, regular blood transfusions, iron accumulation in the tissues, and the adverse effects of medications. Additionally, it poses a significant financial burden on the healthcare system [1–4].

In the past, renal involvement as a complication of β-thalassemia was not widely recognized. However, due to the advancement of iron chelator medications, the life expectancy of individuals with β-thalassemia has notably increased. Consequently, new potential complications such as agranulocytosis, hepatic injuries, endocrine organ diseases, and renal disorders have emerged as possible risks. Emerging evidence suggests that chronic anemia, tissue iron deposition, hemodynamic alterations, and iron chelator medications may be potential etiologies for renal impairments, e.g. glomerulopathy and tubulopathy, in individuals with β-thalassemia [5–11].

Numerous studies present conflicting findings regarding the influence of common iron chelator medications, specifically Deferoxamine, Deferiprone, and Deferasirox, on the glomerular filtration rate (GFR) in individuals with β-thalassemia. However, the majority of these studies highlight diminished GFR levels in patients undergoing Deferasirox treatment. Deferasirox is an orally administered iron chelator designed for once-daily use. It received approval from the United States Food and Drug Administration (FDA) for administration in individuals aged two and above in 2005 and was subsequently introduced in over 90 countries. The compound is generally well-tolerated and is associated with mild to moderate adverse effects, including rash, gastrointestinal discomfort, and a slight elevation in serum creatinine level, which are mostly manageable. In the third phase of the Deferasirox clinical trial, over one-third of the patients who had been administered the drug for one year manifested a mild to moderate elevation in serum creatinine levels. Only a small number of patients had levels that exceeded

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the upper limit of normal. No instances of acute or chronic renal failure were documented during clinical trials. However, a limited number of studies indicate the occurrence of acute kidney injury in patients undergoing Deferasirox treatment [9,11–23].

Deferasirox carries a high risk of nephrotoxicity, which can lead to decreased glomerular filtration, the necessity for dialysis, and dysfunction of the proximal tubular system. Some experts believe that the disadvantages of Deferasirox often outweigh its benefits for most patients. This consideration is particularly important given that other therapies, such as Deferiprone and Deferoxamine, have significantly lower toxicity rates while still offering acceptable efficacy. However, patients tend to tolerate Deferasirox much better than the alternative treatments. Limited information exists about the molecular processes involved in Deferasirox nephrotoxicity; however, research indicates that hemodynamic alterations, mitochondrial swelling and injury, and localized iron deficiency leading to altered ATP synthesis play significant roles [12,24–26].

In clinical practice, renal function assessment often relies on measuring serum creatinine concentration. Nevertheless, various factors notably influence this metric, including nutritional status and muscle mass. Due to the potential changes in body composition observed in β-thalassemia patients, including increased adiposity and decreased lean body mass, serum creatinine level may not be a reliable marker of glomerular function. A more accurate and sensitive marker is clearly needed in this context [23,27,28].

Cystatin-C is a low-molecular-weight protein that belongs to the superfamily of cystatin protease inhibitors. It is produced continuously by all cells in the body and undergoes free filtration in the glomeruli. Compared to creatinine, cystatin-C is a more sensitive and precise marker of glomerular dysfunction, displaying independence from factors such as age, gender, or body mass [29–33]. This study aims to evaluate glomerular function using serum cystatin-C and creatinine levels in transfusion-dependent β-thalassemia undergoing Deferasirox treatment and investigate the related risk factors.

Materials and methods

A descriptive cross-sectional study was conducted at Ali Asghar Children's Center in Tehran, Iran, from March 2023 to January 2024. The study included twenty-seven diagnosed transfusion-dependent β-thalassemia patients undergoing Deferasirox treatment as their iron chelation therapy at 20 mg/kg/day dose. Patients with abnormal urine analysis, irregular radiologic findings in previous kidney ultrasonography, recurrent urinary infections, history of nephrotoxic drugs intake, and those diagnosed with other systemic diseases affecting the kidney, such as diabetes mellitus, were excluded from the study.

The study design, with serial number IR. IUMS. FMD. REC. 1401.513, was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran. Informed consent was directly obtained from participants or their parents.

Patients underwent a comprehensive clinical assessment to procure data on their age, height, weight, duration of Deferasirox intake, frequency of blood transfusions, and history of splenectomy surgery. Before the transfusion, a blood sample was obtained and forwarded for laboratory analyses, encompassing serum levels of BUN, creatinine, cystatin-C, and ferritin. The utilized kit (Cyastin C, Biorex diagnostics®) assessed the serum cystatin-C level using an immunoturbidimetry assay on the Siemens ADIVA 1800 analyzer, with a specified normal range of 0.5 to 1.03 (mg/dL). The cystatin-C assay was calibrated according to the manufacturer's instructions. Serum creatinine was measured by the Jaffe-rate blanket method with a normal range of 0.7 to 1.4 (mg/dL). All measurements were performed in a single certified laboratory (Gholhak Clinical Laboratory) under standardized protocols.

For patients 18 years and older, we calculated the GFR using the CKD-EPI creatinine Equation (2021) and the CKD-EPI Cystatin-C Equation (2012). Individuals under 18 years had their GFR determined using the Creatinine-based 'Bedside Schwartz' Equation (2009) and the Cystatin-C-based Equation (2012). These formulas are widely validated for adult and pediatric populations, respectively, ensuring appropriate eGFR estimation across our study's age range. These computations were conducted using the eGFR Calculator, available on the National Kidney Foundation (NKF) website [34] (https://www.kidney.org). The normal GFR range was assumed to be 90 to 120 ml/min/1.73m^2 [35–41].

Statistical analysis

The data underwent statistical analysis and was presented using various descriptive measures, such as the mean, standard deviation (SD), and range for continuous variables and frequencies and percentages for categorical variables. Comparison of numerical variables between study groups employed the Student t-test for independent samples, while the χ^2 test was utilized for comparing categorical data. Fisher's exact test was employed when the expected frequency was less than 5. Correlation between variables was assessed using the Spearman rank correlation equation. Multiple linear regression analysis was utilized to examine the impacts of independent variables on serum cystatin-C and creatinine levels. The regression model's assumptions were validated, ensuring the appropriateness of the analysis. To address the assumption of residual normality, we applied a square root transformation to the cystatin-C variable, thereby improving the distribution of residuals and enhancing the robustness of the model's findings. The level of statistical significance was set at $p < 0.05$. All statistical analyses were conducted using IBM SPSS Statistics (Version 27) for Microsoft Windows. The tables and figures were created using Microsoft Excel (2013) and IBM SPSS Statistics (Version 27).

Results

Twenty-seven patients, with a mean age of 23.30 ± 8.90 years, were enrolled in the current study. There were 17 (63%)

males and 10 (37%) females. The mean duration of Deferasirox therapy was 9.88 ± 4.92 years in the study group. Twenty-two patients received Deferoxamine as iron chelation therapy prior to initiating Deferasirox, while seven patients were initially treated with Deferasirox. Table 1 provides a concise presentation of demographic and laboratory data for review.

The recorded average serum levels of cystatin-C and creatinine were 1.07 ± 0.23 mg/dL and 0.82 ± 0.18 mg/dL, respectively. According to the manufacturer's guidelines, normal levels for cystatin-C should be less than 1.03 mg/dL, and creatinine should be less than 1.4 mg/dL. As per the defined cutoff criteria, 14 out of 27 patients (51.8%) exhibited elevated levels of serum cystatin-C, while only 1 out of 27 patients (3.7%) demonstrated elevated creatinine levels. No statistically significant difference was observed in the serum levels of cystatin-C ($p = 0.312$) and creatinine ($p = 0.790$) between the male and female subjects.

Patients with elevated serum cystatin-C levels also demonstrate heightened creatinine ($p < 0.001$, 95%CI = 0.117, 0.345) and BUN levels ($p = 0.002$, 95%CI = 1.725, 6.699) and, concurrently, exhibit reduced ferritin levels ($p = 0.023$, 95%CI= −1323.928, −104.717) compared to individuals with normal serum cystatin-C levels. There were no statistically significant differences in sex ($p = 0.440$), age ($p = 0.905$), weight ($p = 0.321$), height ($p = 0.566$), BMI ($p = 0.389$), estimated years of Deferasirox intake ($p = 0.618$), frequency of blood transfusion ($p = 0.597$), and history of splenectomy ($p = 0.863$) between the two groups. Table 2 provides a summary of the comparison between the two groups.

The GFR was calculated using both cystatin-C-based and creatinine-based equations. According to the cystatin-C-based equation, the GFR ranged from 47 to 119, with a mean value of 82.14 ± 19.30. Based on this equation, 11 (40.7%) patients had normal GFR (G1), 13 (48.1%) had mildly decreased GFR (G2), and three (11.1%) had mildly to moderately reduced GFR (G3). For the creatinine-based equation, the GFR showed a mean value of 106.40 ± 21.14 with a range of 62 to 139. According to this equation, 21 (77.8%) patients had normal GFR (G1), and 6 (22.2%) had mildly decreased GFR (G2), while none showed mildly to moderately reduced GFR (G3) (Figure 1).

In the current study, the serum levels of cystatin-C showed a positive correlation with creatinine (r = 0.561, $p = 0.002$), BUN (r = 0.452, $p = 0.018$), and BMI (r = 0.388, $p = 0.046$), and a negative correlation with ferritin (r=-0.515, $p = 0.006$) (Figures 2–5). However, no correlation was observed between cystatin-C levels and age ($p = 0.366$), estimated years of Deferasirox intake ($p = 0.746$), height ($p = 0.697$), weight ($p = 0.198$), and frequency of blood transfusion ($p = 0.633$). Further analysis of the data revealed a positive correlation between serum creatinine and cystatin-C (r = 0.561, $p = 0.002$), BUN (r = 0.402, $p = 0.038$), frequency of blood transfusion (r = 0.458, $p = 0.016$), weight (r = 0.555, $p = 0.002$), height (r = 0.452, $p = 0.018$), and BMI (r = 0.488, $p = 0.010$). However, no correlation was found between creatinine and ferritin ($p = 0.168$), age ($p = 0.174$), and estimated years of Deferasirox intake ($p = 0.194$).

The results of the multiple regression analysis showed that only ferritin ($p = 0.003$) had a statistically significant effect on cystatin-C levels, with a negative association. Other variables, including age ($p = 0.450$), sex ($p = 0.936$), weight ($p = 0.766$), height ($p = 0.718$), duration of Deferasirox use ($p = 0.522$), blood transfusion frequency ($p = 0.880$), and splenectomy history ($p = 0.173$), did not significantly impact cystatin-C levels. The results of the multiple regression

Table 1. The main demographic and laboratory data of patients.

Patients characteristics	Number (%)	
Sex		
• Male	17 (63%)	
• Female	10 (37%)	
Splenectomy		
• Yes	12 (44.4%)	
• No	15 (55.6%)	
	Mean ± SD	**Range**
Age (years)	23.30 ± 8.90	4–38
Weight (kg)	54.89 ± 14.66	16–75
Height (cm)	163.26 ± 21.82	95–190
BMI (kg/m^2)	20.09 ± 2.23	16.32 – 24.53
Cystatin-C (mg/dL)	1.07 ± 0.23	0.70 – 1.70
Creatinine (mg/dL)	0.82 ± 0.18	0.50 – 1.47
BUN (mg/dL)	13.31 ± 3.74	8.20 – 21.50
Ferritin (ng/dL)	1186.43 ± 836.74	162.70–3,298
Transfusion frequency (per month)	1.74 ± 0.44	1–2
Deferasirox therapy duration (years)	9.88 ± 4.92	3–18

Table 2. Comparison between patients with elevated cystatin-C and normal level.

	Elevated Cystatin-C level	Normal Cystatin-C level			
	Mean ± SD		Mean difference	t	*P* value
Age (years)	23.50 ± 9.89	23.08 ± 8.08	0.423	0.121	0.905
Weight (kg)	57.64 ± 16.34	51.92 ± 12.58	5.720	1.013	0.321
Height (cm)	165.64 ± 22.84	160.69 ± 21.27	4.951	0.581	0.566
BMI (kg/m^2)	20.45 ± 2.48	19.70 ± 1.94	7.5698	0.877	0.389
Transfusion frequency (per month)	1.78 ± 0.42	1.69 ± 0.48	0.0934	0.536	0.597
Deferasirox therapy duration (years)	10.35 ± 4.78	9.38 ± 5.22	0.97253	0.505	0.618
Creatinine (mg/dL)	0.93 ± 0.18	0.70 ± 0.06	0.23132	4.307	<0.001
BUN (mg/dL)	15.34 ± 3.99	11.13 ± 1.78	4.21209	3.579	0.002
Ferritin (ng/dL)	842.5 ± 257.91	1556.8 ± 1076.23	714.32308	2.332	0.023
	Numbers (Frequency)				***P* value**
Sex					0.440
• Male	10 (37%)	7 (26%)			
• Female	4 (15%)	6 (22%)			
Splenectomy					0.863
• Yes	6 (22%)	6 (22%)			
• No	8 (30%)	7 (26%)			

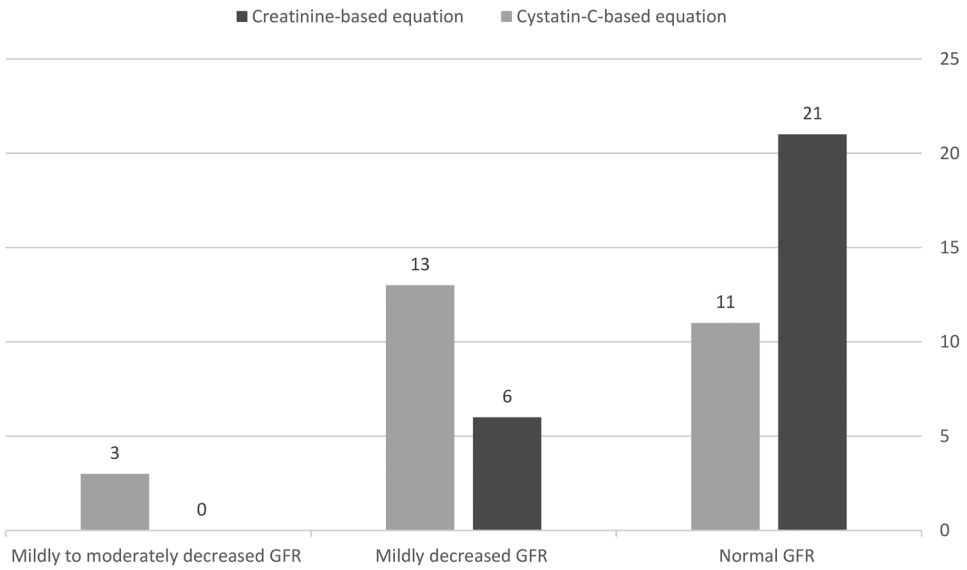

Figure 1. Calculated GFR using cystatin-C-based and creatinine-based equations.

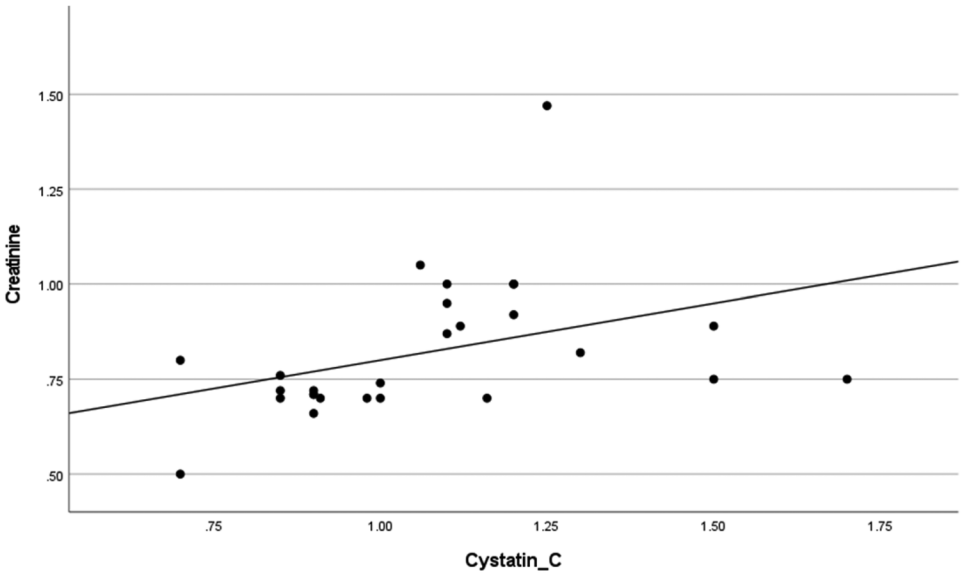

Figure 2. Correlation between cystatin-C and creatinine.

analysis to examine the effect of various factors on creatinine levels showed that none of the independent variables, including sex ($p = 0.160$), age ($p = 0.305$), weight ($p = 0.441$), height ($p = 0.912$), duration of Deferasirox consumption ($p = 0.754$), blood transfusion frequency ($p = 0.479$), ferritin levels ($p = 0.159$), and splenectomy history ($p = 0.637$), had a statistically significant impact on creatinine levels.

Discussion

Before the introduction of iron chelation therapies, patients with β-thalassemia had a low life expectancy and often faced premature death due to severe cardiac iron build-up. Because of this, they did not typically experience conditions such as renal impairments. Nowadays, with increased life expectancy, renal disorders are one of the leading causes of morbidity in β-thalassemia patients, possibly due to chronic anemia and hypoxia, iron overload, and chelation therapy. Uzun *et al.* reported observable changes in glomerular and tubular markers among patients with both major and intermedia β-thalassemia when compared to those with minor β-thalassemia and the healthy control group. Additionally, they found that levels of serum cystatin-C were elevated in the minor β-thalassemia group in comparison to the control group. This indicates that the disease itself, irrespective of influences such as blood transfusions and chelation therapy, may pose a risk for glomerular impairment [5,29,42].

Iron chelation therapy has been identified as a known risk factor for the development of renal insufficiency [5,43]. In 2012, Basma *et al.* conducted a case-control study to investigate the renal function in β-thalassemia patients. They found that β-thalassemia patients undergoing iron chelation therapy with Deferoxamine exhibited significantly higher levels of serum cystatin-C and creatinine, as well as a

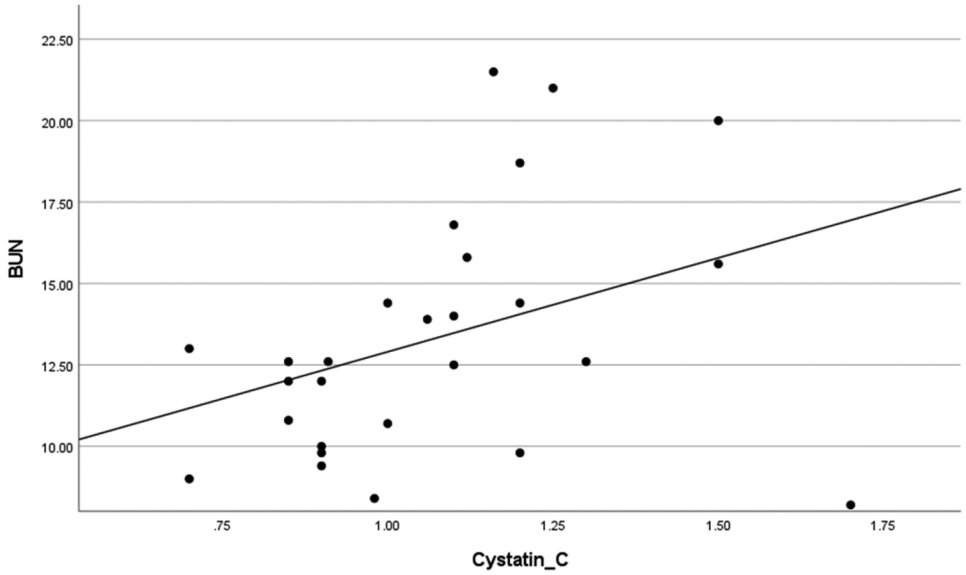

Figure 3. Correlation between cystatin-C and BUN.

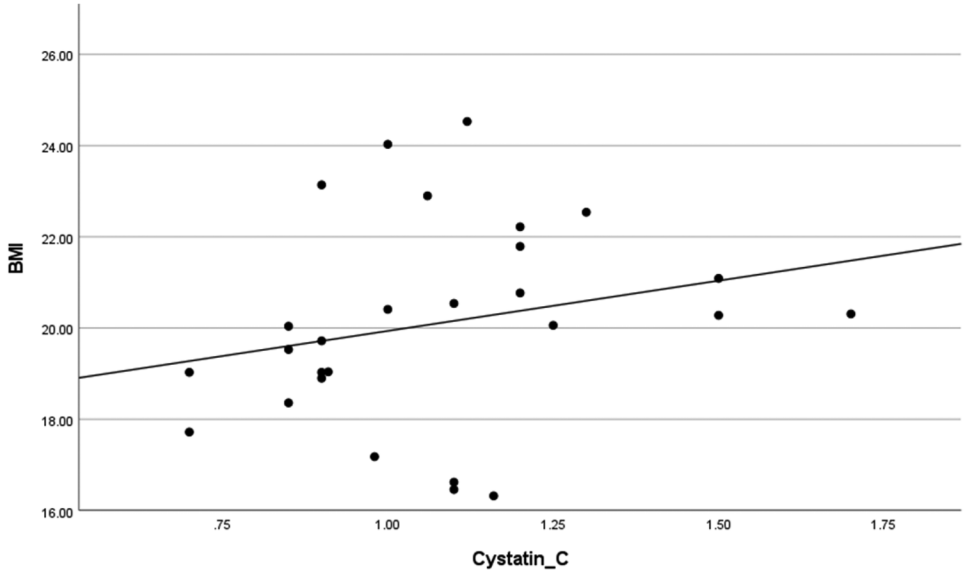

Figure 4. Correlation between cystatin-C and BMI.

decrease in GFR, compared to β-thalassemia patients who did not receive iron chelation therapy and the healthy control group [44]. Several studies suggest that Deferasirox is more likely to be associated with renal impairment compared to Deferoxamine and Deferiprone [30]. Osama *et al.* conducted a longitudinal study to examine the glomerular and tubular function in patients with β-thalassemia. The study compared patients treated with Deferasirox to those who received Deferoxamine with or without Deferiprone. The results showed that patients who received Deferasirox had significantly higher serum creatinine levels and reduced GFR than those who received other chelation therapies [21]. Annayev *et al.* conducted a similar study in Italy. They report that cystatin-C, an indicator of renal function, was significantly higher in the patients' group receiving Deferasirox compared to the group receiving Deferiprone and the control group. However, there was no significant difference between the Deferiprone and control groups [22].

Here, we investigate glomerular function by analyzing cystatin-C and creatinine levels in β-thalassemia patients receiving Deferasirox treatment. Our analysis revealed that the mean serum cystatin-C level stood at 1.07 ± 0.23 mg/dL, with 51.8% of the patients exhibiting levels surpassing the established normal range. In previous studies, Gokce *et al.*, Hamdy *et al.*, Annayev *et al.*, Papassotiriou *et al.*, and Voskaridou *et al.* observed elevated levels of serum cystatin-C in 64.7%, 59.5%, 50%, 44%, and 40% of their patients, respectively [11,22,29,45,46]. In the present study, only 1 (3.7%) patient exhibited elevated serum creatinine levels, consistent with Cappellini *et al.*, who reported a 3% incidence during the phase III assessment of Deferasirox [13]. Relevant studies reported similar findings; either no or only

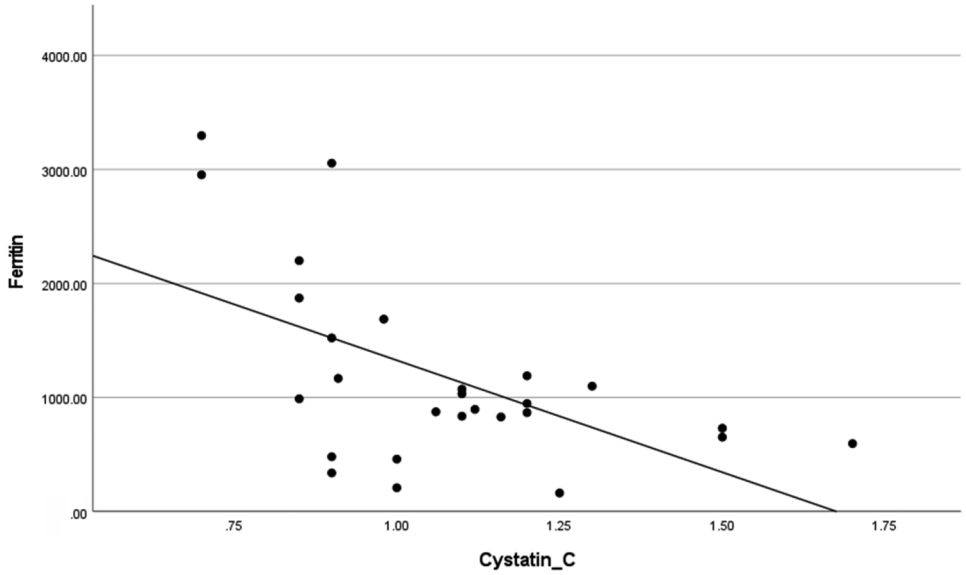

Figure 5. Correlation between cystatin-C and ferritin.

a limited number of patients had elevated serum creatinine, while the mean serum creatinine level in the patient groups was significantly higher compared to the control groups [22,45,47].

The serum creatinine level alone is not a reliable measure of renal function because it can be affected by factors such as muscle mass and nutritional status. Even if the serum creatinine level is within the normal range, the GFR could decrease by half. This is especially noticeable in patients with β-thalassemia due to potential changes in their body composition [27,29,45,48]. Several studies have reported glomerular hyperfiltration in β-thalassemia patients, as determined by estimated GFR calculated using creatinine-based equations. Some of these studies suggest that creatinine may not serve as a reliable indicator of renal function in β-thalassemia patients, possibly due to their reduced body mass and high prevalence of malnourishment. Alternatively, other studies state that documented glomerular hyperfiltration may indicate increased renal plasma flow, resulting from decreased systemic vascular resistance due to chronic anemia [22,29,30,45,49–51]. In our study, glomerular hyperfiltration (eGFR > 120 ml/min/1.73m$^{2)}$ was observed in 26% of patients using the creatinine-based equation to calculate GFR. However, none of our patients showed an increased glomerular filtration rate when utilizing the cystatin-C equation. Based on this equation, 59% of patients in the current study had reduced GFR. We believe these findings suggest that cystatin-C may take priority over creatinine as an indicator for GFR in this group of patients, rather than reflecting hemodynamic changes.

Papassotiriou and colleagues conducted a study in Greece involving 150 β-thalassemia patients who received Deferasirox for nine months. The study revealed that these patients exhibited normal renal function yet concurrently displayed elevated levels of cystatin-C. The researchers declared that these findings suggest hemodynamic alterations attributed to Deferasirox rather than renal impairment. They also observed increased levels of neutrophil gelatinase-associated lipocalin (NGAL) as an indicator of tubular injuries [11]. The findings correspond with those of González *et al.*, who noted that the intraperitoneal administration of Deferasirox chelating therapy in normal rats resulted in direct nephrotoxic effects on epithelial tubular cells, while glomerular function remained unaffected [12]. Annayev *et al.* reported that Deferasirox may lead to dose-dependent tubulopathy. The study revealed that 28% of their patients exhibited higher urine calcium to creatinine (Ca/Cr) ratios and a significant increase in urinary β2 microglobulin (Uβ2MG) compared to the control group. Both elevated Ca/Cr ratios and increased Uβ2MG levels are recognized as indicators of tubular injury [22]. Similarly, Sadeghi *et al.* discovered proximal tubular abnormalities among 166 subjects with β-thalassemia major. Notably, their urinary excretion levels of protein, calcium, phosphorus, uric acid, magnesium, and β2-microglobulin surpassed those of the general healthy population [52]. In the current study, we did not assess tubular function in our selected group of patients.

In our research, we have observed strong positive correlations among cystatin-C, creatinine, and BUN, all of which indicate renal function. Notably, patients exhibiting elevated levels of cystatin-C also displayed higher BMI; however, no correlation was found between cystatin-C and height or weight. Shankar *et al.* conducted a study encompassing 2,583 healthy adults, aiming to explore the correlation between cystatin-C and BMI. The findings underscore a positive association between increased BMI levels and elevated cystatin-C levels, serving as an early indicator of renal impairment. Additionally, the researchers emphasized that heightened cystatin-C levels can serve as a predictive marker for potential hypertension, diabetes mellitus, and increased cardiovascular mortality risk [53]. The current study identified a negative correlation between cystatin-C and ferritin levels. The results of the multiple regression analysis also indicated that ferritin is the only variable with a statistically significant impact on cystatin-C levels, with a p values of 0.003, demonstrating a negative association. Similar findings

were reported by Al-Khabori *et al.*, who identified a weak linear relationship between ferritin and the estimated glomerular filtration rate (eGFR) using cystatin-C. They propose that the potentially diminished eGFR may be attributed to iron's direct nephrotoxic impact, chelation therapy's influence, or a combination of both. Lastly, they discussed the confounding nature of serum ferritin and highlighted the potential bias introduced by chelation therapy in the analyses [30]. Other studies have reported conflicting findings regarding the correlation between cystatin-C and ferritin, with some finding a positive correlation [11,44,47,50] and some finding no significant correlation [22,23,29]. Basma *et al.* and Premadi *et al.* have independently established a positive correlation between cystatin-C and ferritin in their respective studies. They propose that iron accumulation can lead to hemosiderosis and result in kidney damage [44,50]. Uzun *et al.* identified a significant positive correlation between serum ferritin levels and various markers of tubular and glomerular function, including fractional excretion of sodium (FENa), retinol-binding protein (RBP), α-1-microglobulin, Uβ2MG, cystatin-C levels, and the urinary protein-to-creatinine ratio. They propose that increased iron accumulation in the body may be linked to an elevated risk of glomerular and tubular dysfunction [22]. Moreover, Papassotiriou and colleagues have also documented a positive correlation between these parameters in β-thalassemia patients undergoing Deferasirox treatment. However, they propose an alternative interpretation, suggesting that these observed correlations may be indicative of hemodynamic changes rather than renal impairment [11]. As ferritin is a known acute-phase reactant, its levels can change during inflammatory states. In our study, participants were screened to ensure they were not experiencing any acute inflammatory conditions when blood samples were taken [54]. Our observations suggest a negative correlation between cystatin-C and ferritin levels, which may indicate a nephrotoxic effect associated with chelation therapy. We propose that lower ferritin levels may be a reliable indicator of a patient's adherence to Deferasirox therapy. This aligns with the theory that Deferasirox can be nephrotoxic, potentially causing local iron deficiency in renal cells and leading to cell death by disrupting ATP production pathways [24,55]. Gottwald *et al.* reported that the toxicity induced by Deferasirox is diminished when the drug binds to proteins such as ferritin and albumin in vivo. These findings imply that lower ferritin levels could correspond to higher free drug levels and a more significant nephrotoxic effect [26]. Our findings, which indicate a negative association between ferritin and serum cystatin-C levels, support this theory.

In our current study, all patients received the same dose of chelation therapy, which prevented us from investigating its impact on renal function. Conversely, Gokce *et al.* conducted a study on 71 β-thalassemia subjects in Turkey, wherein they documented a negative correlation between Deferasirox dosage and cystatin-C levels. Their findings suggested that the influence of relative iron depletion on renal function outweighs the direct nephrotoxic effects of chelation therapy [45]. As a matter of investigating iron chelation therapy's impact on renal function, we initially anticipated a positive correlation between cystatin-C and the duration of Deferasirox therapy. However, the results turned out to be insignificant. In contrast, Basma *et al.* found that serum cystatin-C showed a highly significant positive correlation with the duration of chelation therapy [44].

The current research has certain limitations as a cross-sectional study. It is not feasible to follow subjects or establish a cause-and-effect relationship. Furthermore, the number of participants was limited due to narrow inclusion criteria. We recommend that more comprehensive studies be planned, and inulin clearance as a preferred method to estimate GFR [32] and tubular markers such as Uβ2MG and urinary NGAL should be considered.

Conclusion

In summary, subclinical renal impairment is a recognized complication in patients with β-thalassemia. This condition may be associated with chronic hypoxia, iron overload, and chelation therapies, particularly Deferasirox. Furthermore, serum creatinine levels are considered an unreliable indicator of renal function in this patient population due to creatinine's inherent limitations and the unique pathophysiological characteristics of the disease. We strongly encourage the implementation of regular monitoring of serum cystatin-C levels every six months for patients with β-thalassemia undergoing Deferasirox treatment. This proactive screening strategy is essential to ensure optimal patient outcomes and effectively manage potential therapy complications.

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Data availability statement

The data supporting this study's findings are available from the corresponding author, H. Akbarnataj, upon reasonable request.

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